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(54) Title: HIGH EFFICIENCY GENE TRANSFER AND EXPRESSION IN MAMMALIAN CELLS BY A MULTIPLE TRANS-FECTION PROCEDURE OF MAR SEQUENCES

(57) Abstract: The present invention relates to purified and isolated DNA sequences having protein production increasing activity and more specifically to the use of matrix attachment regions (MARs) for increasing protein production activity in a eukaryotic cell. Also disclosed is a method for the identification of said active regions, in particular MAR nucleotide sequences, and the use of these characterized active MAR sequences in a new multiple transfection method.

HIGH EFFICIENCY GENE TRANSFER AND EXPRESSION IN MAMMALIAN CELLS BY A MULTIPLE TRANSFECTION PROCEDURE OF MAR SEQUENCES

FIELD OF THE INVENTION

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The present invention relates to purified and isolated DNA sequences having protein production increasing activity and more specifically to the use of matrix attachment regions (MARs) for increasing protein production activity in a eukaryotic cell. Also disclosed is a method for the identification of said active regions, in particular MAR nucleotide sequences, and the use of these characterized active MAR sequences in a new multiple transfection method.

BACKGROUND OF THE INVENTION

Nowadays, the model of loop domain organization of eukaryotic chromosomes is well accepted (Boulikas T, "Nature of DNA sequences at the attachment regions of genes to the nuclear matrix", J. Cell Biochem., 52:14-22, 1993). According to this model chromatin is organized in loops that span 50-100 kb attached to the nuclear matrix, a proteinaceous network made up of RNPs and other nonhistone proteins (Bode J, Stengert-Iber M, Kay V, Schalke T and Dietz-Pfeilstetter A, Crit. Rev. Euk. Gene Exp., 6:115-138, 1996).

The DNA regions attached to the nuclear matrix are termed SAR or MAR for respectively scaffold (during metaphase) or matrix (interphase) attachment regions (Hart C and Laemmli U (1998), "Facilitation of chromatin dynamics by SARs" Curr Opin Genet Dev 8, 519-525.)

As such, these regions may define boundaries of independent chromatin do mains, such that only the encompassing cis-regulatory elements control the expression of the genes within the domain.

However, their ability to fully shield a chromosomal locus from nearby chromatin

elements, and thus confer position-independent gene expression, has not been seen in stably transfected cells (Poliak L. Seum C. Mattioni T and Laemmli U. (1994) "SARs stimulate but do not confer position independent gene expression". Nucleic Acids Res 35 22, 4386-4394). On the other hand, MAR (or S/MAR) sequences have been shown to interact with enhancers to increase local chromatin accessibility (Jenuwein T, Forrester W. Fernandez-Herrero L. Laible G. Dull M. and Grosschedl R. (1997) "Extension of chromatin accessibility by nuclear matrix attachment regions" Nature 385, 269-272). 40 Specifically, MAR elements can enhance expression of heterologous genes in cell culture lines (Kalos M and Fournier R (1995) "Position-independent transgene expression mediated by boundary elements from the apolipoprotein B chromatin domain" Mol Cell Biol 15.198-207), transgenic mice (Castilla J, Pintado B, Sola, I, Sanchez-Morgado J. and Enjuanes L (1998) "Engineering passive immunity in 45 transgenic mice secreting virus-neutralizing antibodies in milk" Nat Biotechnol 16, 349-354) and plants (Allen G. Hall GJ. Michalowski S, Newman W, Spiker S, Weissinger A, and Thompson W (1996), "High-level transgene expression in plant cells: effects of a strong scaffold attachment region from tobacco" Plant Cell 8, 899-913). The utility of MAR sequences for developing improved vectors for gene therapy is also recognized (Agarwal M, Austin T, Morel F, Chen J, Bohnlein E, and Plavec I (1998), "Scaffold 50 attachment region-mediated enhancement of retroviral vector expression in primary T

cells" J Virol 72, 3720-3728).

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Recently, it has been shown thatchromatin-structure modifying sequences including MARs, as exemplified by the chicken lysozyme 5' MAR is able to significantly enhance reporter expression in pools of stable Chinese Hamster Ovary (CHO) cells (Zahn-Zabal M. et al., "Development of stable cell lines for production or regulated expression using matrix attachment regions" J Biotechnol, 2001, 87(1): p. 29-42). This property was used to increase the proportion of high-producing clones, thus reducing the number of clones that need to be screened. These benefits have been observed both for constructs with MARs flanking the transgene expression cassette, as well as when constructs are cotransfected with the MAR on a separate plasmid. However, expression levels upon cotransfection with MARs were not as high as those observed for a construct in which two MARs delimit the transgene expression unit. A third and preferable process was shown to be the transfection of transgenes with MARs both linked to the transgene and on a separate plasmid (Girod et al., submitted for publication). However, one persisting limitation of this technique is the quantity of DNA that can be transfected per cell. Many multiples transfection protocols have been developed in order to achieve a high transfection efficiency to characterize the function of genes of interest. The protocol applied by Yamamoto et al, 1999 ("High efficiency gene transfer by multiple transfection protocol", Histochem. J. 31(4), 241-243) leads to a transfection efficiency of about 80 % after 5 transfections events, whereas the conventional transfection protocol only achieved a rate of <40%. While this technique may be useful when one wishes to increase the proportion of expressing cells, it does not lead to cells with a higher intrinsic productivity. Therefore, it cannot be used to generate high producer monoclonal cell lines. Hence, the previously described technique has two major drawbacks:

 this technique does not generate a homogenous population of transfected cells, since it cannot favour the integration of further gene copy, nor does it direct the transgenes to favorable chromosomal loci,

 ii) the use of the same selectable marker in multiple transfection events does not permit the selection of doubly or triply transfected cells.

In patent application WO02/074969, the utility of MARs for the development of stable eukaryotic cell lines has also been demonstrated. However, this application does not disclose neither any conserved homology for MAR DNA element nor any technique for predicting the ability for a DNA sequence to be a MAR sequence.

In fact no clear-cut MAR consensus sequence has been found (Boulikas T, "Nature of DNA sequences at the attachment regions of genes to the nuclear matrix", *J. Cell Biochem.*, 52:14-22, 1993) but evolutionarily, the structure of these sequences seem to be functionally conserved in eukaryotic genomes, since animal MARs can bind to plant nuclear scaffolds and vice versa (Mielke C, Kohwi Y, Kohwi-Shigematsu T and Bode J, "Hierarchical binding of DNA fragments derived from scaffold-attached regions: correlation of properties in vitro and function in vivo", *Biochemistry*, 29:7475-7485, 1990).

The identification of MARs by biochemical studies is a long and unpredictable process; various results can be obtained depending on the assay (Razin SV, "Functional architecture of chromosomal DNA domains", *Crit Rev Eukaryot Gene Expr.*, 6:247-269, 1996). Considering the huge number of expected MARs in a eukaryotic genome and the amount of sequences issued from genome projects, a tool able to filter potential MARS in order to perform targeted experiments would be greatly useful.

Currently two different predictive tools for MARs are available via the Internet. The fist one, MAR-Finder (http://futuresoft.org/MarFinder: Singh GB, Kramer JA and Krawetz SA, "Mathematical model to predict regions of chromatin attachment to the nuclear matrix", Nucleic Acid Research, 25:1419-1425, 1997) is based on set of patterns identified within several MARs and a statistical analysis of the co-occurrence of these patterns. MAR-Finder predictions are dependent of the sequence context, meaning that predicted MARs depend on the context of the submitted sequence. The other predictive software, SMARTest (http://www. genomatix.de; Frisch M, Frech K. Klingenhoff A, Cartharius K, Liebich I and Werner T, "In silico prediction of scaffold/matrix attachment regions in large genomic sequences". Genome Research. 12:349-354, 2001), use weight-matrices derived from experimentally identified MARs. SMARTest is said to be suitable to perform large-scale analyses. But actually aside its relative poor specificity, the amount of hypothetical MARs rapidly gets huge when doing large scale analyses with it, and in having no way to increase its specificity to restrain the number of hypothetical MARs, SMARTest becomes almost useless to screen for potent MARs form large DNA sequences.

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Some other softwares, not available via the Internet, also exists; they are based as well on the frequency of MAR motifs (MRS criterion;Van Drunen CM et al., "A bipartite sequence element associated with matrix/scaffold attachment regions", *Nucleic Acids Res*, 27:2924-2930, 1999), (Chrclass; Glazko GV et al., "Comparative study and prediction of DNA fragments associated with various elements of the nuclear matrix", *Biochim. Biophys. Acta*, 1517:351-356, 2001) or based on the identification of sites of stress-induced DNA duplex (SIDD; Benham C and al., "Stress-induced duplex DNA destabilization in scaffold/matrix attachment regions", *J. Mol. Biol.*, 274:181-196, 1997). However, their suitability to analyze complete genome sequences remains unknown, and whether these tools may allow the identification of protein production-increasing sequences has not been reported.

Furthermore, due to the relatively poor specificity of these softwares (Frisch M, Frech K, Klingenhoff A, Cartharius K, Liebich I and Werner T, "In silico prediction of scaffold/matrix attachment regions in large genomic sequences", *Genome Research*, 12:349-354, 2001), the amount of hypothetical MARs identified in genomes rapidly gets unmanageable when doing large scale analyses, especially if most of these have no or poor activity in practice. Thus, having no way to increase prediction specificity to restrain the number of hypothetical MARs, many of the available programs become almost useless to identify potent genetic elements in view of efficiently increasing recombinant protein production.

Since all the above available predictive methods have some drawbacks that prevent large-scale analyses of genomes to identify reliably novel and potent MARs, the object of this invention is to 1) understand the functional features of MARs that allow improved recombinant protein expression; 2) get a new Bioinformatic tool compiling MAR structural features as a prediction of function, in order to 3) perform large scale analyses of genomes to identify novel and more potent MARs, and, finally 4) to demonstrate improved efficiency to increase the production of recombinant proteins from eukarvotic cells or organisms when using the newly identified MAR sequences.

SUMMARY OF THE INVENTION

This object has been achieved by providing an improved and reliable method for the identification of DNA sequences having protein production increasing activity, in

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PCT/EP2004/011974 particular MAR nucleotide sequences, and the use of these characterized active MAR sequences in a new multiple transfection method to increase the production of recombinant proteins in eukarvotic cells.

BRIFF DESCRIPTION OF THE FIGURES

Fig. 1 shows the distribution plots of MARs and non-MARs sequences. Histograms are density plots (relative frequency divided by the bin width) relative to the score of the observed parameter. The density histogram for human MARs in the SMARt DB database is shown in black, while the density histogram for the human chromosome 22 are in grev.

Fig. 2 shows Scatterplots of the four different criteria used by SMAR Scan® and the AT-content with human MARs from SMARt DB.

Fig. 3 shows the distribution plots of MAR sequences by organism. MAR sequences from SMARt DB of other organisms were retrieved and analyzed. The MAR sequences density distributions for the mouse, the chicken, the sorghum bicolor and the human are plotted jointly.

Fig. 4 shows SMAR Scan® predictions on human chromosome 22 and on shuffled chromosome 22. Top plot : Average number of hits obtained by SMAR Scan® with five: rubbled, scrambled, shuffled within nonoverlapping windows of 10 bp, order 1 Markov chains model and with the native chromosome 22. Bottom plot: Average number of MARs predicted by SMAR Scan® in five: rubbled, scrambled, shuffled within nonoverlapping windows of 10 bp, order 1 Markov chains model and with the native chromosome 22.

Fig. 5 shows the dissection of the ability of the chicken lysozyme gene 5'-MAR to 30 stimulate transgene expression in CHO-DG44 cells. Fragments B. K and F show the highest ability to stimulate transgene expression. The indicated relative strength of the elements was based on the number of high-expressor cells.

Fig. 6 shows the effect of serial-deletions of the 5'-end (upper part) and the 3'-end 35 (lower part) of the 5'-MAR on the loss of ability to stimulate transgene expression. The transition from increased to decreased activity coincide with B-, K- and F-fragments.

Fig. 7 shows that portions of the F fragment significantly stimulate transgene expression. The F fragment regions indicated by the light grey arrow were multimerized, inserted in pGEGFP Control and transfected in CHO cells. The element that displays the highest activity is located in the central part of the element and corresponds to fragment FIII (black bar labelled minimal MAR). In addition, an enhancer activity is located in the 3'-flanking part of the FIII fragment (dark grey bar labelled MAR enhancer).

Fig. 8 shows a map of locations for various DNA sequence motifs within the cLysMAR. Fig. 8 (B) represents a Map of locations for various DNA sequence motifs within the cLysMAR. Vertical lines represent the position of the computer-predicted sites or sequence motifs along the 3034 base pairs of the cLysMAR and its active regions, as presented in Fig. 5. The putative transcription factor sites. (MEF2 05, Oct-1, USF-02, GATA, NFAT) for activators and (CDP, SATB1, CTCF, ARBP/MeCP2) for repressors of transcription, were identified using MatInspector (Genomatix), and CpG islands were identified with CPGPLOT. Motifs previously associated with MAR elements are labelled

in black and include CpG dinucleotides and CpG islands, unwinding motifs (AATATAT and AATATT), poly As and Ts, poly Gs and Cs, Drosophila topoisomerase II binding sites (GTNWAYATTNATTNATNNR) which had identity to the 6 bp core and High mobility group I (HMG-I/Y) protein binding sites. Other structural motifs include nucleosome-binding and nucleosome disfavouring sites and a motif thought to relieve the superhelical strand of DNA. Fig. 8(A) represents the comparison of the ability of portions of the cLysMAR to activate transcription with MAR prediction score profiles with MarFinder. The top diagram shows the MAR fragment activity as in Fig. 5, while the middle and bottom curves show MARFinder-predicted potential for MAR activity and 10 for bent DNA structures respectively.

Fig. 9 shows the correlation of DNA physico-chemical properties with MAR activity. Fig. 9(A), represents the DNA melting temperature, double helix bending, major grove depth and minor groove width profiles of the 5'-MAR and were determined using the algorithms of Levitsky et al (Levitsky VG, Ponomarenko MP, Ponomarenko JV, Frolov AS, Kolchanov NA "Nucleosomal DNA property database", *Bioinformatics*, 15; 582592, 1999). The most active B, K and F fragments depicted at the top are as shown as in Figure 1. Fig. 9(B), represents the enlargement of the data presented in panel A to display the F fragment map aligned with the tracings corresponding to the melting temperature (top curve) and DNA bending (bottom curve). The position of the most active FIB fragment and protein binding site for specific transcription factors are as indicated.

Fig. 10 shows the distribution of putative transcription factor binding sites within the 5'25 cLysMAR. Large arrows indicate the position of the CUE elements as identified with SMAR Scan®.

Fig. 11 shows the scheme of assembly of various portions of the MAR. The indicated portions of the cLysMAR were amplified by PCR, introducing BgIII-BamHI linker elements at each extremity, and assembled to generate the depicted composite elements. For instance, the top construct consists of the assembly of all CUE and flanking sequences at their original location except that BgII-BamHII linker sequences separate each element.

35 Fig. 12 represents the plasmid maps.

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Fig. 13 shows the effect of re-transfecting primary transfectants on GFP expression. Cells (CHO-DG44) were co-transfected with pSV40EGFP (left tube) or pMAR-SV40EGFP (central tube) and pSVneo as resistance plasmid. Cells transfected with pMAR-SV40EGFP were re-transfected 24 hours later with the same plasmid and a different selection plasmid, pSVpuro (right tube). After two weeks selection, the phenotype of the stably transfected cell population was analysed by FACS.

Fig. 14 shows the effect of multiple load of MAR-containing plasmid. The pMAR-SV40EGFP/ pMAR-SV40EGFP secondary transfectants were used in a third cycle of transfection at the end of the selection process. The tertiary transfection was accomplished with pMAR or pMAR-SV40EGFP to give tertiary transfectants. After 24 hours, cells were transfected again with either plasmid, resulting in the quaternary transfectants (see Table 4).

Fig. 15 shows comparative performance of SMAR prediction algorithms exemplified by region WP18A10A7. (A) SMAR Scan® analysis was performed with default settings. (B) SIDD analysis (top curve and left-hand side scale), and the attachment of several

DNA fragments to the nuclear matrix in vitro (bar-graph, right-hand side scale) was taken from Goetze et al (Goetze S, Gluch A, Benham C, Bode J, "Computational and in vitro analysis of destabilized DNA regions in the interferon gene cluster: potential of predicting functional gene domains." *Biochemistry*, 42:154-166, 2003).

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Fig. 16 represents the results of a a gene therapy-like protocol using MARs. The group of mice injected by MAR-network, induced from the beginning of the experiment, display a better induction of the hematocrit in comparison of mice injected by original network without MAR. After 2 months, hematocrits in "MAR-containing group" is still at values higher (65%) than normal hematocrit levels (45-55%).

Fig. 17 represents the scatterplot for the 1757 S/MAR sequences of the AT (top) and TA (bottom) dinucleotide percentages versus the predicted DNA bending as computed by SMAR Scan®.

Fig. 18 represents the dinucleotide percentage distribution plots over the 1757 non-S/MARs sequences.

20 Fig.19 shows the effect of various S/MAR elements on the production of recombinant green fluorescent protein (GFP). Populations of CHO cells transfected with a GFP expression vector containing or a MAR element, as indicated, were analyzed by a fluorescence-activated cell sorter (FACS®), and typical profiles are shown. The profiles display the cell number counts as a function of the GFP fluorescence levels.

Fig. 20 depicts the effect of the induction of hematocrit in mice injected by MAR-network.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a purified and isolated DNA sequence having protein production increasing activity characterized in that said DNA sequence comprises at least one bent DNA element, and at least one binding site for a DNA binding protein.

Certain sequences of DNA are known to form a relatively "static curve", where the DNA follows a particular 3-dimensional path. Thus, instead of just being in the normal B-DNA conformation ("straight"), the piece of DNA can form a flat, planar curve also defined as bent DNA (Marini, et al., 1982 "Bent helical structure in kinetoplast DNA", Proc. Natl. Acad. Sci. USA. 79: 7664-7664).

Surprisingly, Applicants have shown that the bent DNA element of a purified and isolated DNA sequence having protein production increasing activity of the present invention usually contains at least 10% of dinucleotide TA, and/or at least 12% of dinucleotide AT on a stretch of 100 contiguous base pairs. Preferably, the bent DNA element contains at least 33% of dinucleotide TA, and/or at least 33% of dinucleotide AT on a stretch of 100 contiguous base pairs. These data have been obtained by the method described further.

50 According to the present invention, the purified and isolated DNA sequence usually comprises a MAR nucleotide sequence selected from the group comprising the sequences SEQ ID Nos 1 to 27 or a cLysMAR element or a fragment thereof. Preferably, the purified and isolated DNA sequence is a MAR nucleotide sequence

WO 2005/040377 PCT/EP2004/011974 selected from the group comprising the sequences SEQ ID Nos 1 to 27, more preferably the sequences SEQ ID Nos 24 to 27.

Encompassed by the present invention are as well complementary sequences of the above-mentioned sequences SEQ ID Nos 1 to 27 and the cLysMAR element or fragment, which can be produced by using PCR or other means.

An "element" is a conserved nucleotide sequences that bears common functional properties (i.e. binding sites for transcription factors) or structural (i.e. bent DNA sequence) features.

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A part of sequences SEQ ID Nos 1 to 27 and the cLysMAR element or fragment refers to sequences sharing at least 70% nucleotides in length with the respective sequence of the SEQ ID Nos 1 to 27. These sequences can be used as long as they exhibit the same properties as the native sequence from which they derive. Preferably these sequences share more than 80%, in particular more than 90% nucleotides in length with the respective sequence of the SEQ ID Nos 1 to 27.

The present invention also includes variants of the aforementioned sequences SEQ ID Nos 1 to 27 and the cLysMAR element or fragment, that is nucleotide sequences that vary from the reference sequence by conservative nucleotide substitutions, whereby one or more nucleotides are substituted by another with same characteristics.

The sequences SEQ ID Nos 1 to 23 have been identified by scanning human chromosome 1 and 2 using SMAR Scan®, showing that the identification of novel MAR sequences is feasible using the tools reported thereafter whereas SEQ ID No 24 to 27 have been identified by scanning the complete human genome using the combined SMAR Scan® method.

30 In a first step, the complete chromosome 1 and 2 were screened to identify bent DNA element as region corresponding to the highest bent, major groove depth, minor groove width and lowest melting temperature as shown in figure 3. In a second step, this collection of sequence was scanned for binding sites of regulatory proteins such as SATB1, GATA, etc. as shown in the figure 8B) yielding sequences SEQ ID 1-23. Furthermore, sequences 21-23 were further shown to be located next to known gene from the Human Genome Data Base.

With regard to SEQ ID No 24 to 27 these sequences have been yielded by scanning the human genome according to the combined method and were selected as examples among 1757 MAR elements so detected.

Molecular chimera of MAR sequences are also considered in the present invention. By molecular chimera is intended a nucleotide sequence that may include a functional portion of a MAR element and that will be obtained by molecular biology methods known by those skilled in the art.

Particular combinations of MAR elements or fragments or sub-portions thereof are also considered in the present invention. These fragments can be prepared by a variety of methods known in the art. These methods include, but are not limited to, digestion with restriction enzymes and recovery of the fragments, chemical synthesis or polymerase chain reactions (PCR).

Therefore, particular combinations of elements or fragments of the sequences SEQ ID

Nos 1 to 27 and cLysMAR elements or fragments are also envisioned in the present invention, depending on the functional results to be obtained. Elements of the cLysMAR are e.g. the B, K and F regions as described in WO 02/074969, the disclosure of which is hereby incorporated herein by reference, in its entirety. The preferred elements of the cLysMAR used in the present invention are the B, K and F regions. Only one element might be used or multiple copies of the same or distinct elements (multimerized elements) might be used (see Fig. 8 A)).

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By fragment is intended a portion of the respective nucleotide sequence. Fragments of a MAR nucleotide sequence may retain biological activity and hence bind to purified nuclear matrices and/or alter the expression patterns of coding sequences operably linked to a promoter. Fragments of a MAR nucleotide sequence may range from at least about 100 to 1000 bp, preferably from about 200 to 700 bp, more preferably from about 300 to 500 bp nucleotides. Also envisioned are any combinations of fragments, which have the same number of nucleotides present in a synthetic MAR sequence consisting of natural MAR element and/or fragments. The fragments are preferably assembled by linker sequences, Preferred linkers are BdIII-BamHI linker.

"Protein production increasing activity" refers to an activity of the purified and isolated DNA sequence defined as follows: after having been introduced under suitable conditions into a eukaryotic host cell, the sequence is capable of increasing protein production levels in cell culture as compared to a culture of cell transfected without said DNA sequence. Usually the increase is 1.5 to 10 fold, preferably 4 to 10 fold. This corresponds to a production rate or a specific cellular productivity of at least 10 pg per cell per day (see Example 11 and Fig. 13).

As used herein, the following definitions are supplied in order to facilitate the understanding of this invention.

30 "Chromatin" is the protein and nucleic acid material constituting the chromosomes of a eukaryotic cell, and refers to DNA, RNA and associated proteins.

A "chromatin element" means a nucleic acid sequence on a chromosome having the property to modify the chromatine structure when integrated into that chromosome.

"Cis" refers to the placement of two or more elements (such as chromatin elements) on the same nucleic acid molecule (such as the same vector, plasmid or chromosome).

"Trans" refers to the placement of two or more elements (such as chromatin elements) on two or more different nucleic acid molecules (such as on two vectors or two chromosomes).

Chromatin modifying elements that are potentially capable of overcoming position effects, and hence are of interest for the development of stable cell lines, include boundary elements (BEs), matrix attachment regions (MARs), locus control regions (LCRs), and universal chromatin opening elements (UCOEs).

Boundary elements ("BEs"), or insulator elements, define boundaries in chromatin in many cases (Bell A and Felsenfeld G. 1999; "Stopped at the border: boundaries and insulators, Curr Opin Genet Dav 9, 191-198) and may play a role in defining a transcriptional domain in vivo. BEs lack intrinsic promoter/enhancer activity, but rather are thought to protect genes from the transcriptional influence of regulatory elements in the surrounding chromatin. The enhancer-block assay is commonly used to identify

insulator elements. In this assay, the chromatin element is placed between an enhancer and a promoter, and enhancer-activated transcription is measured. Boundary elements have been shown to be able to protect stably transfected reporter genes against position effects in Drosophila, yeast and in mammalian cells. They have also been shown to increase the proportion of transgenic mice with inducible transgene expression.

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Locus control regions ("LCRs") are cis-regulatory elements required for the initial chromatin activation of a locus and subsequent gene transcription in their native locations (Grosveld, F. 1999, "Activation by locus control regions?" *Curr Opin Genet Dev* 9, 152-157). The activating function of LCRs also allows the expression of a coupled transgene in the appropriate tissue in transgenic mice, irrespective of the site of integration in the host genome. While LCRs generally confer tissue-specific levels of expression on linked genes, efficient expression in nearly all tissues in transgenic mice has been reported for a truncated human T-cell receptor LCR and a rat LAP LCR. The most extensively characterized LCR is that of the globin locus. Its use in vectors for the gene therapy of sickle cell disease and (3-thalassemias is currently being evaluated.

"MARs", according to a well-accepted model, may mediate the anchorage of specific DNA sequence to the nuclear matrix, generating chromatin loop domains that extend 20 outwards from the heterochromatin cores. While MARs do not contain any obvious consensus or recognizable sequence, their most consistent feature appears to be an overall high A/T content, and C bases predominating on one strand (Bode J, Schlake T, RiosRamirez M. Mielke C. Stengart M. Kay V and KlehrWirth D. "Scaffold/matrixattached regions: structural propreties creating transcriptionally active loci". Structural 25 and Functional Organization of the Nuclear Matrix: International Review of Citology. 162A:389453, 1995). These regions have a propensity to form bent secondary structures that may be prone to strand separation. They are often referred to as baseunpairing regions (BURs), and they contain a core-unwinding element (CUE) that might 30 represent the nucleation point of strand separation (Benham C and al., Stress induced duplex DNA destabilization in scaffold/matrix attachment regions, J. Mol. Biol., 274:181-196, 1997). Several simple AT-rich sequence motifs have often been found within MAR sequences, but for the most part, their functional importance and potential mode of action remain unclear. These include the A-box (AATAAAYAAA), the T-box 35 (TTWTWTTWTT), DNA unwinding motifs (AATATATT, AATATT), SATB1 binding sites (H-box, A/T/C25) and consensus Topoisomerase II sites for vertebrates (RNYNNCNNGYNGKTNYNY) or Drosophila (GTNWAYATTNATNNR).

Ubiquitous chromatin opening elements ("UCOEs", also known as "ubiquitously-acting chromatin opening elements") have been reported in WO 00/05393.

An "enhancer" is a nucleotide sequence that acts to potentiate the transcription of genes independent of the identity of the gene, the position of the sequence in relation to the gene, or the orientation of the sequence. The vectors of the present invention optionally include enhancers.

A "gene" is a deoxyribonucleotide (DNA) sequence coding for a given mature protein. As used herein, the term "gene" shall not include untranslated flanking regions such as RNA transcription initiation signals, polyadenylation addition sites, promoters or enhancers.

A "product gene" is a gene that encodes a protein product having desirable characteristics such as diagnostic or therapeutic utility. A product gene includes, e. g.,

structural genes and regulatory genes.

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A "structural gene" refers to a gene that encodes a structural protein. Examples of structural genes include but are not limited to, cytoskeletal proteins, extracellular matrix proteins, enzymes, nuclear pore proteins and nuclear scaffold proteins, ion channels and transporters, contractile proteins, and chaperones. Preferred structural genes encode for antibodies or antibody fragments.

A "regulatory gene" refers to a gene that encodes a regulatory protein. Examples of regulatory proteins include, but are not limited to, transcription factors, hormones, growth factors, cytokines, signal transduction molecules, oncogenes, proto-oncogenes, transmembrane receptors, and protein kinases.

"Orientation" refers to the order of nucleotides in a given DNA sequence. For example, an inverted orientation of a DNA sequence is one in which the 5' to 3' order of the sequence in relation to another sequence is reversed when compared to a point of reference in the DNA from which the sequence was obtained. Such reference points can include the direction of transcription of other specified DNA sequences in the source DNA and/or the origin of replication of replicable vectors containing the sequence.

"Eukaryotic cell" refers to any mammalian or non-mammalian cell from a eukaryotic organism. By way of non-limiting example, any eukaryotic cell that is capable of being maintained under cell culture conditions and subsequently transfected would be included in this invention. Especially preferable cell types include, e. g., stem cells, embryonic stem cells, Chinese hamster ovary cells (CHO), COS, BHK21, NIH3T3, HeLa, C2C12, cancer cells, and primary differentiated or undifferentiated cells. Other suitable host cells are known to those skilled in the art.

30 The terms "host cell" and "recombinant host cell" are used interchangeably herein to indicate a eukaryotic cell into which one or more vectors of the invention have been introduced. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

The terms "introducing a purified DNA into a eukaryotic host cell" or "transfection" denote any process wherein an extracellular DNA, with or without accompanying material, enters a host cell. The term "cell transfected" or "transfected cell" means the cell into which the extracellular DNA has been introduced and thus harbours the extracellular DNA. The DNA might be introduced into the cell so that the nucleic acid is replicable either as a chromosomal interarant or as an extra chromosomal element.

45 "Promoter" as used herein refers to a nucleic acid sequence that regulates expression of a gene.

"Co-transfection" means the process of transfecting a eukaryotic cell with more than one exogenous gene, or vector, or plasmid, foreign to the cell, one of which may confer a selectable phenotype on the cell.

The purified and isolated DNA sequence having protein production increasing activity also comprises, besides one or more bent DNA element, at least one binding site for a DNA binding protein.

Usually the DNA binding protein is a transcription factor. Examples of transcription factors are the group comprising the polyQpolyP domain proteins.
 Another example of a transcription factor is a transcription factor selected from the group comprising SATB1, NMP4, MEF2, S8, DLX1, FREAC7, BRN2, GATA 1/3, TATA, Bright, MSX, AP1, C/EBP, CREBP1, FOX, Freac7, HFH1, HNF3alpha, Nkx25,
 POU3F2, Pit1, TTF1, XFD1, AR, C/EBPgamma, Cdc5, FOXD3, HFH3, HNF3 beta, MRF2, Oct1, POU6F1, SRF, V\$MTATA_B, XFD2, Bach2, CDP CR3, Cdx2, FOXJ2, HFL, HP1, Myc, PBX, Pax3, TEF, VBP, XFD3, Brn2, COMP1, Evil, FOXP3, GATA4, HFN1, Lhx3, NKX3A, POU1F1, Pax6, TFIIA or a combination of two or more of these transcription factors are preferred. Most preferred are SATB1, NMP4, MEF2 and pol/QpolyP domain proteins.

SATB1, NMP4 and MEF2, for example, are known to regulate the development and/or tis sue-specific gene expression in mammals. These transcription factors have the capacity to alter DNA geometry, and reciprocally, binding to DNA as an allosteric ligand modifies their structure. Recently, SATB1 was found to form a cage-like structure circumscribing heterochromatin (Cai S, Han HJ, and Kohwi-Shigematsu T, "Tissue-specific nuclear architecture and gene expression regulated by SATB1" Nat Genet, 2003, 34(1): p. 42-51).

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- Yet another object of the present invention is to provide a purified and isolated cLysMAR element and/or fragment, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- 30 More preferably, the cLysMAR element and/or fragment are consisting of at least one nucleotide sequence selected from the B, K and F regions.
- A further object of the present invention is to provide a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences.

Preferably, the synthetic MAR sequence comprises a cLysMAR element and/or fragment a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants. Also preferably, linker sequences are BqIII-BamHI linker.

An other aspect of the invention is to provide a method for identifying a MAR sequence using a Bioinformatic tool comprising the computing of values of one or more DNA sequence features corresponding to DNA bending, major groove depth and minor groove width potentials and melting temperature. Preferably, the identification of one or more DNA sequence features further comprises a further DNA sequence feature corresponding to binding sites for DNA binding proteins, which is also computed with this method.

50 Preferably, profiles or weight-matrices of said bioinformatic tool are based on dinucleotide recognition.

The bioinformatic tool used for the present method is preferably, SMAR Scan®, which contains algorithms developed by Gene Express (http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wgetz">http://lsrs6bin/cgibin/wge

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Preferably, SMAR Scan® uses the four theoretical criteria also designated as DNA sequence features corresponding to DNA bending, major groove depth and minor groove width potentials, melting temperature in all possible combination, using scanning windows of variable size (see Fig. 3). For each function used, a cut-off value has to be set. The program returns a hit every time the computed score of a given region is above the set cut-off value for all of the chosen criteria. Two data output modes are available to handle the hits, the first (called "profile-like") simply returns all hit positions on the query sequence and their corresponding values for the different criteria chosen. The second mode (called "contiguous hits") returns only the positions of several contiguous hits and their corresponding sequence. For this mode, the minimum number of contiguous hits is another cut-off value that can be set, again with a tunable window size. This second mode is the default mode of SMAR Scan®. Indeed, from a semantic point of view, a hit is considered as a core-unwinding element (CUE), and a cluster of CUEs accompanied by clusters of binding sites for relevant proteins is considered as a MAR. Thus, SMAR Scan® considers only several contiquous hits as a potential MAR.

To tune the default cut-off values for the four theoretical structural criteria, experimentally validated MARs from SMARt DB (http://transfac.gbf.de/- SMARt DB) were used. All the human MAR sequences from the database were retrieved and analyzed with SMAR Scan® using the "profile-like" mode with the four criteria and with no set cut-off value. This allowed the setting of each function for every position of the sequences. The distribution for each criterion was then computed according to these data (see Fig. 1 and 3).

The default cut-off values of SMAR Scan® for the bend, the major groove depth and the minor groove width were set at the average of the 75th quantile and the median. For the melting temperature, the default cut-off value should be set at the 75th quantile. The minimum length for the "contiguous-hits" mode should be set to 300 because it is assumed to be the minimum length of a MAR (see Fig. 8 and 9). However, one skilled in the art would be able to determine the cut-off values for the above-mentioned criteria for a given organism with minimal experimentation.

40 Preferably, DNA bending values are comprised between 3 to 5 ° (radial degree). Most preferably they are situated between 3.8 to 4.4 °, corresponding to the smallest peak of Fig. 1.

Preferably the major groove depth values are comprised between 8.9 to 9.3 Å (Angström) and minor groove width values between 5.2 to 5.8 Å. Most preferably the major groove depth values are comprised between 9.0 to 9.2 Å and minor groove width values between 5.4 to 5.7 Å.

Preferably the melting temperature is comprised between 55 to 75 ° C (Celsius degree). Most preferably, the melting temperature is comprised between 55 to 62 ° C.

The DNA binding protein of which values can be computed by the method is usually a transcription factor preferably a polyQpolyP domain or a transcription factor selected

from the group comprising SATB1, NMP4, MEF2, S8, DLX1, FREAC7, BRN2, GATA 1/3, TATA, Bright, MSX, AP1, C/EBP, CREBP1, FOX, Freac7, HFH1, HNF3alpha, Nkx25, POU3F2, Pit1, TTF1, XFD1, AR, C/EBPgamma, Cdc5, FOXD3, HFH3, HNF3 beta, MRF2, Oct1, POU6F1, SRF, V\$MTATA_B, XFD2, Bach2, CDP CR3, Cdx2, FOXJ2, HFL, HP1, Myc, PBX, Pax3, TEF, VBP, XFD3, Bm2, COMP1, Evil, FOXP3, GATA4, HFN1, Lhx3, NKX3A, POU1F1, Pax6, TFIIA or a combination of two or more of these transcription factors.

However, one skilled in the art would be able to determine other kinds of transcription factors in order to carry out the method according to the present invention.

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In case SMAR Scan® is envisaged to perform, for example, large scale analysis, then, preferably, the above-mentioned method further comprises at least one filter predicting DNA binding sites for DNA transcription factors in order to reduce the computation.

The principle of this method combines SMAR Scan® to compute the structural features as described above and a filter, such as for example, the pfsearch, (from the pftools package as described in Bucher P, Karplus K, Moeri N, and Hofmann K, "A flexible search technique based on generalized profiles", *Computers and Chemistry*, 20:324, 1996) to predict the binding of some transcription factors.

Examples of filters comprise, but are not limited to, pfsearch, MatInspector, RMatch Professional and TRANSFAC Professional

This combined method uses the structural features of SMAR Scan® and the predicted binding of specific transcription factors of the filter that can be applied sequentially in any order to select MARs, therefore, depending on the filter is applied at the beginning or at the end of the method.

The first level selects sequences out of the primary input sequence and the second level, consisting in the filter, may be used to restrain among the selected sequences those which satisfy the criteria used by the filter.

In this combined method the filter detects clusters of DNA binding sites using profiles or weightmatrices from, for example, Matinspector (Quandt K, Frech K, Karas H, Wingender E, Wemer T, "Matthd and Matinspector New fast and versatile tools for detection of consensus matches in nucleotide sequence data", *Nucleic Acids Research*, 23, 48784884, 1995.). The filter can also detect densities of clusters of DNA binding sites.

The combined method is actually a "wrapper" written in Perl for SMAR Scan® and, in case the pfsearch is used as a filter, from the pftools. The combined method performs a twolevel processing using at each level one of these tools (SMAR Scan® or filter) as a potential "filter", each filter being optional and possible to be used to compute the predicted features without doing any filtering.

If SMAR Scan® is used in the first level to filter subsequences, it has to be used with the "all the contiguous hits" mode in order to return sequences. If the pfsearch is used in the first level as first filter, it has to be used with only one profile and a distance in nucleotide needs to be provided. This distance is used to group together pfsearch hits that are located at a distance inferior to the distance provided in order to return sequences; The combined method launches pfsearch, parses its output and returns

sequences corresponding to pfsearch hits that are grouped together according to the distance provided. Then whatever the tool used in the first level, the length of the subsequences thus selected can be systematically extended at both ends according to a parameter called "hits extension".

The second and optional level can be used to filter out sequences (already filtered sequences or unfiltered input sequences) or to get the results of SMAR Scan® and/or pfsearch without doing any filtering on these sequences. If the second level of combined method is used to filter, for each criteria considered cutoff values (hit per nucleotide) need to be provided to filter out those sequences (see Fig. 20).

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Another concern of the present invention is also to provide a method for identifying a MAR sequence comprising at least one filter detecting clusters of DNA binding sites using profiles or weightmatrices. Preferably, this method comprises two levels of filters and in this case, SMAR Scan® is totally absent from said method. Usually, the two levels consist in prearch.

Also embraced by the present invention is a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter.

Analysis by the combined method of the whole human genome yielded a total of 1757 putative MARs representing a total of 1 065 305 base paires. In order to reduce the number of results, a dinucleotide analysis was performed on these 1757 MARs, computing each of the 16 possible dinucleotide percentage for each sequence considering both strands in the 5' to 3' direction.

Surprisingly, Applicants have shown that all of the "super" MARs detected with the combined method contain at least 10% of dinucleotide TA on a stretch of 100 contiguous base pairs. Preferably, these sequences contain at least 33% of dinucleotide TA on a stretch of 100 contiguous base pairs.

Applicants have also shown that these same sequences further contain at least 12% of dinucleotide AT on a stretch of 100 contiguous base pairs. Preferably, they contain at least 33% of dinucleotide AT on a stretch of 100 contiguous base pairs.

An other aspect of the invention is to provide a purified and isolated MAR DNA sequence of any of the preceding described MARs, comprising a sequence selected from the sequences SEQ ID Nos 1 to 27, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.

Preferably, said purified and isolated MAR DNA sequence comprises a sequence selected from the sequences SEQ ID Nos 24 to 27, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants. These sequences 24 to 27 correspond to those detected by the combined method and show a higher protein production increasing activity over sequences 1 to 23.

The present invention also encompasses the use of a purified and isolated DNA sequence comprising a first isolated matrix attachment region (MAR) nucleotide sequence which is a MAR nucleotide sequence selected from the group comprising

a purified and isolated DNA sequence having protein production increasing

- a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter,
- the sequences SEQ ID Nos 1 to 27.

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- a purified and isolated cLysMAR element and/or fragment,
- a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences,
- a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants or a MAR nucleotide sequence of a cLysMAR element and/or fragment, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants for increasing protein production activity in a eukaryotic host cell. 15

Said purified and isolated DNA sequence usually further comprises one or more regulatory sequences, as known in the art e.g. a promoter and/or an enhancer, polyadenylation sites and splice junctions usually employed for the expression of the protein or may optionally encode a selectable marker. Preferably said purified and isolated DNA sequence comprises a promoter which is operably linked to a gene of interest.

The DNA sequences of this invention can be isolated according to standard PCR 25 protocols and methods well known in the art.

Promoters which can be used provided that such promoters are compatible with the host cell are, for example, promoters obtained from the genomes of viruses such as polyoma virus, adenovirus (such as Adenovirus 2), papilloma virus (such as bovine papilloma virus), avian sarcoma virus, cytomegalovirus (such as murine or human cytomega lovirus immediate early promoter), a retrovirus, hepatitis-B virus, and Simian Virus 40 (such as SV 40 early and late promoters) or promoters obtained from heterologous mammalian promoters, such as the actin promoter or an immunoglobulin promoter or heat shock promoters. Such regulatory sequences direct constitutive expression.

Furthermore, the purified and isolated DNA sequence might further comprise regulatory sequences which are capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting 40 examples of suitable tissue-specific promoters include the albumin promoter (liverspecific: Pinkert et al., 1987, Genes Dev.1; 268-277), lymphoid-specific promoters (Calame and Eaton, 1988, Adv. Immunol, 43; 235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989, EMBOJ, 8; 729-733) and immunoglobulins (Banerii, etal., 1983, Cell 33: 729-740; Queen and Baltimore, 1983, Cell 33:741-748), 45 neuron-specific promoters (e. g., the neurofilament promoter; Byme and Ruddle, 1989. Proc.Natl. Acad. Sci. USA 86: 5473-5477), pancreas-specific promoters (Edlund, et al., 1985. Science 230: 912-916), and mammary gland-specific promoters (e. g., milk whey promoter; U. S. Pat. No. 4,873,316 and European Application No. 264,166). 50

Developmentally-regulated promoters are also encompassed. Examples of such promoters include, e.g., the murine hox promoters (Kessel and Gruss, 1990. Science 249: 374-379) and thea-fetoprotein promoter (Campes and Tilghman, 1989. Genes

Dev. 3: 537-546).

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Regulatable gene exp ression promoters are well known in the art, and include, by way of non-limiting example, any promoter that modulates expression of a gene encoding a desired protein by binding an exogenous molecule, such as the CRE/LOX system, the TET system, the doxycycline system, the NFkappaB/UV light system, the Leu3p/isopropylmalate system, and theGLVPc/GAL4 system (See e. g., Sauer, 1998, Methods 14 (4): 381-92; Lewandoski, 2001, Nat. Rev. Genet 2 (10): 743-55; Legrand-Poels et al., 1998, J. Photochem. Photobiol. B. 45: 18; Guo et al., 1996, FEBS Lett. 390 (2): 191-5; Wang et al., PNAS USA, 1999,96 (15): 84838). However, one skilled in the art would be able to determine other kinds of promoters that are suitable in carrying out the present invention.

Enhancers can be optionally included in the purified DNA sequence of the invention then belonging to the regulatory sequence, e.g. the promoter.

The "gene of interest" or "transgene" preferably encodes a protein (structural or regulatory protein). As used herein "protein" refers generally to peptides and polypeptides having more than about ten amino acids. The proteins may be "homologous" to the host (i.e., endogenous to the host cell being utilized), or "heterologous," (i.e., foreign to the host cell being utilized), such as a human protein produced by yeast. The protein may be produced as an insoluble aggregate or as a soluble protein in the periplasmic space or cytoplasm of the cell, or in the extracellular medium. Examples of proteins include hormones such as growth hormone or erytropoletin (EPO), growth factors such as epidemal growth factor, analgesic substances like enkephalin, enzymes like chymotrypsin, receptors to hormones or growth factors, antibodies and include as well proteins usually used as a visualizing marker e.g. green fluorescent protein.

30 Preferably the purified DNA sequence further comprises at least a second isolated matrix attachment region (MAR) nucleotide sequence selected from the group comprising

- a purified and isolated DNA sequence having protein production increasing
- a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter,
 - the sequences SEQ ID Nos 1 to 27,
 - a purified and isolated cLysMAR element and/or fragment,
 - a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences.

a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants. The isolated matrix attachment region (MAR) nucleotide sequence might be identical or different.

45 Alternatively, a first and a second identical MAR nucleotide sequence are used.

Preferably, the MAR nucleotide sequences are located at both the 5' and the 3' ends of the sequence containing the promoter and the gene of interest. But the invention also envisions the fact that said first and or at least second MAR nucleotide sequences are located on a sequence distinct from the one containing the promoter and the gene of interest

PCT/EP2004/011974 Embraced by the scope of the present invention is also the purified and isolated DNA

sequence comprising a first isolated matrix attachment region (MAR) nucleotide sequence which is a MAR nucleotide sequence selected from the group comprising

a purified and isolated DNA sequence having protein production increasing activity.

- a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool. the combined method or the method comprising at least one filter,
- the sequences SEQ ID Nos 1 to 27.

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- a purified and isolated cLysMAR element and/or fragment,
 - a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences,

a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants that can be used for increasing protein production activity in a eukaryotic host cell by introducing the purified and isolated DNA sequence into a eukaryotic host cell according to well known protocols. Usually applied methods for introducing DNA into eukaryotic host cells applied are e.g. direct introduction of cloned DNA by microinjection or microparticle bombardment: electrotransfer :use of viral vectors: encapsulation within a carrier system; and use of transfecting reagents such as calcium phosphate, diethylaminoethyl (DEAE) -dextran or commercial transfection systems like the Lipofect-AMINE 2000 (Invitrogen). Preferably, the transfection method used to introduce the purified DNA sequence into a eukaryotic host cell is the method for transfecting a eukaryotic cell as described below.

The purified and isolated DNA sequence can be used in the form of a circular vector. Preferably, the purified and isolated DNA sequence is used in the form of a linear DNA sequence as vector.

As used herein, "plasmid" and "vector" are used interchangeably, as the plasmid is the 30 most commonly used vector form. However, the invention is intended to include such other forms of expression vectors, including, but not limited to, viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions. 35

The present invention further encompasses a method for transfecting a eukaryotic host cell, said method comprising

- a) introducing into said eukarvotic host cell at least one purified DNA sequence comprising at least one DNA sequence of interest and/or at least one purified and isolated DNA sequence comprising a MAR nucleotide sequence or other chromatin modifying elements,
- b) subjecting within a defined time said transfected eukaryotic host cell to at least one additional transfection step with at least one purified DNA sequence comprising at least one DNA sequence of interest and/or with at least one purified and isolated DNA sequence comprising a MAR nucleotide sequence or other chromatin modifying elements
- c) selecting said transfected eukaryotic host cell.

Preferably at least two up to four transfecting steps are applied in step b).

In order to select the successful transfected cells, a gene that encodes a selectable marker (e. g., resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. The gene that encodes a selectable marker might be located

on the purified DNA sequence comprising at least one DNA sequence of interest and/or at least one purified and isolated DNA sequence consisting of a MAR nucleotide sequence or other chromatin modifying elements or might optionally be co-introduced in separate form e.g. on a plasmid. Various selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. The amount of the drug can be adapted as desired in order to increase productivity

Usually, one or more selectable markers are used. Preferably, the selectable markers used in each distinct transfection steps are different. This allows selecting the transformed cells that are "multi-transformed" by using for example two different antibiotic selections.

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Any eukaryotic host cell capable of protein production and lacking a cell wall can be used in the methods of the invention. Examples of useful mammalian host cell lines include human cells such as human embryonic kidney line (293 or 293 cells subcloned 15 for growth in suspension culture, Graham et al., J. Gen Virol 36, 59 (1977)), human cervical carcinoma cells (HELA, ATCC CCL 2), human lung cells (W138, ATCC CCL 75), human liver cells (Hep G2, HB 8065); rodent cells such as baby hamster kidnev cells (BHK, ATCC CCL 10), Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77, 4216 (1980)), mouse sertoli cells (TM4, Mather, 20 Biol. Reprod 23, 243-251 (1980)), mouse mammary tumor (MMT 060562, ATCC CCL51); and cells from other mammals such as monkey kidney CV1 line transformed by SV4O (COS-7, ATCC CRL 1651); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); canine kidney cells (MDCK. ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); myeloma (e.g. NS0) 25 /hybridoma cells.

Preferably, the selected transfected eukaryotic host cells are high protein producer cells with a production rate of at least 10 pg per cell per day.

Most preferred for uses herein are mammalian cells, more preferred are CHO cells.

The DNA sequence of interest of the purified and isolated DNA sequence is usually a gene of interest preferably encoding a protein operably linked to a promoter as

gene of interest preferably encoding a protein operably linked to a promoter as described above. The purified and isolated DNA sequence comprising at least one DNA sequence of interest might comprise additionally to the DNA sequence of interest MAR nucleotide sequence or other chromatin modifying elements.

Purified and isolated DNA sequence comprising a MAR nucleotide sequence are for example selected from the group comprising the sequences SEQ ID Nos 1 to 27 and/or particular elements of the cLysMAR e.g. the B, K and F regions as well as fragment and elements and combinations thereof as described above. Other chromatin modifying elements are for example boundary elements (BEs), locus control regions (LCRs), and universal chromatin opening elements (UCOEs) (see Zahn-Zabal et al. already cited). An example of multiple transfections of host cells is shown in Example 12 (Table 3). The first transfecting step (primary transfection) is carried out with the gene of interest (SV40EGFP) alone, with a MAR nucleotide sequence (MAR-SV40EGFP). The second transfecting step (secondary transfection) is carried out with the gene of interest (SV40EGFP) alone, with a MAR nucleotide sequence (MAR) alone or with the gene of interest in the properties of the sequence (MAR) alone or with the gene of interest and a MAR nucleotide sequence (MAR-SV40EGFP), in all possible combinations resulting from the first transfecting step.

Preferably the eukaryotic host cell is transfected by:

 a) introducing a purified DNA sequence comprising one DNA sequence of interest and additionally a MAR nucleotide sequence,

b) subjecting within a defined time said transfected eukaryotic host cell to at least one additional transfection step with the same purified DNA sequence comprising one DNA sequence of interest and additionally a MAR nucleotide sequence of step a).

Also preferably, the MAR nucleotide sequence of the of the purified and isolated DNA sequence is selected form the group comprising

- a purified and isolated DNA sequence having protein production increasing activity,
- a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter,
- the sequences SEQ ID Nos 1 to 27,

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- a purified and isolated cLysMAR element and/or fragment.
- a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences,

a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.

Surprisingly, a synergy between the first and second transfection has been observed. A particular synergy has been observed when MAR elements are present at one or both of the transfection steps. Multiple transfections of the cells with pMAR alone or in combination with various expression plasmids, using the method described above have been carried out. For example, Table 3 shows that transfecting the cells twice with the pMAR-SV40EGFP plasmid gave the highest expression of GFP and the highest degree of enhancement of all conditions (4.3 fold). In contrast, transfecting twice the vector without MAR gave little or no enhancement, 2.8-fold, instead of the expected two-fold increase. This proves that the presence of MAR elements at each transfection step is of particular interest to achieve the maximal protein synthesis.

As a particular example of the transfection method, said purified DNA sequence comprising at least one DNA sequence of interest can be introduced in form of multiple unlinked plasmids, comprising a gene of interest operably linked to a promoter, a selectable marker gene, and/or protein production increasing elements such as MAR sequences.

The ratio of the first and subsequent DNA sequences may be adapted as required for the use of specific cell types, and is routine experimentation to one ordinary skilled in the art.

The defined time for additional transformations of the primary transformed cells is tightly dependent on the cell cycle and on its duration. Usually the defined time corresponds to intervals related to the cell division cycle.

Therefore this precise timing may be adapted as required for the use of specific cell types, and is routine experimentation to one ordinary skilled in the art.

Preferably the defined time is the moment the host cell just has entered into the same phase of a second or a further cell division cycle, preferably the second cycle.

This time is usually situated between 6h and 48 h, preferably between 20h and 24h after the previous transfecting event.

Also encompassed by the present invention is a method for transfecting a eukaryotic host cell, said method comprising co-transfecting into said eukaryotic host cell at least one first purified and isolated DNA sequence comprising at least one DNA sequence of

interest, and a second purified DNA comprising at least one MAR nucleotide selected from the group comprising:

- a purified and isolated DNA sequence having protein production increasing
- a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter.
- the sequences SEQ ID Nos 1 to 27.

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- a purified and isolated cLysMAR element and/or fragment,
- a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences.

a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants. Said first purified and isolated DNA sequence can also comprise at least one MAR

nucleotide as described above. Also envisioned is a process for the production of a protein wherein a eukaryotic host cell is transfected according to the transfection methods as defined in the present invention and is cultured in a culture medium under conditions suitable for expression of the protein. Said protein is finally recovered according to any recovering process known to the skilled in the art.

Given as an example, the following process for protein production might be used. The eukaryotic host cell transfected with the transfection method of the present invention is used in a process for the production of a protein by culturing said cell under 25 conditions suitable for expression of said protein and recovering said protein. Suitable culture conditions are those conventionally used for in vitro cultivation of eukaryotic cells as described e.g. in WO 96/39488. The protein can be isolated from the cell culture by conventional separation techniques such as e.g. fractionation on immunoaffinity or ion-exchange columns; precipitation; reverse phase HPLC; chromatography; chromatofocusing; SDS-PAGE; gel filtration. One skilled in the art will appreciate that purification methods suitable for the polypeptide of interest may require modification to account for changes in the character of the polypeptide upon expression in recombinant cell culture.

The proteins that are produced according to this invention can be tested for 35 functionality by a variety of methods. For example, the presence of antigenic epitopes and ability of the proteins to bind ligands can be determined by Western blot assays. fluorescence cell sorting assays, immunoprecipitation, immunochemical assays and/or competitive binding assays, as well as any other assay which measures specific binding 40 activity.

The proteins of this invention can be used in a number of practical applications including but not limited to:

- 1. Immunization with recombinant host protein antigen as a viral/pathogen antagonist.
- 2. Production of membrane proteins for diagnostic or screening assays.
 - Production of membrane proteins for biochemical studies.
 - Production of membrane protein for structural studies.
- 5. Antigen production for generation of antibodies for immuno-histochemical mapping, including mapping of orphan receptors and ion channels.

Also provided by the present invention is a eukarvotic host cell transfected according to any of the preceding transfection methods. Preferably, the eukaryotic host cell is a mammalian host cell line.

As already described, example of useful marmmalian host cell lines include human cells such as human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol 36, 59 (1977)), human cervical carcinoma cells (HELA, ATCC CCL 2), human lung cells (W138, ATCC CCL 75), human liver cells (Hep G2, HB 8065); rodent cells such as baby hamster kidney cells (BHK, ATCC CCL 10), Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77, 4216 (1980)), mouse sertoli cells (TM4, Mather, Biol. Reprod 23, 243-251 (1980)), mouse mammany tumor (MMT 060562, ATCC CCL51); and cells from other mammals such as monkey kidney CV1 line transformed ySV4O (COS-7, ATCC CRL 1651); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); myeloma (e.g. NS0) /hybridoma cells.

Most preferred for uses herein are CHO cells.

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The present invention also provides for a cell transfection mixture or Kit comprising at least one purified and isolated DNA sequence according to the invention.

The invention further comprises a transgenic organism wherein at least some of its cells have stably incorporated at least one DNA sequence of

- a purified and isolated DNA sequence having protein production increasing activity.
- a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter.
- the sequences SEQ ID Nos 1 to 27.
- a purified and isolated cLvsMAR element and/or fragment.
- a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences.
- a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants. Preferably, some of the cells of the transgenic organisms have been transfected according the methods described herein.
- 35 Also envisioned in the present invention is a transgenic organism wherein its genome has stably incorporated at least one DNA sequence of
 - a purified and isolated DNA sequence having protein production increasing activity.
 - a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter.
 - the sequences SEQ ID Nos 1 to 27,
 - a purified and isolated cLysMAR element and/or fragment,
 - a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences.

a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.

Transgenic eukaryotic organisms which can be useful for the present invention are for example selected form the group comprising mammals (mouse, human, monkey etc) and in particular laboratory animals such as rodents in general, insects (drosophila,

etc), fishes (zebra fish, etc.), amphibians (frogs, newt, etc..) and other simpler organisms such as c. elegans, yeast, etc....

Yet another object of the present invention is to provide a computer readable medium comprising computer-executable instructions for performing the method for identifying a MAR sequence as described in the present invention.

The foregoing description will be more fully understood with reference to the following Examples. Such Examples, are, however, exemplary of methods of practising the present invention and are not intended to limit the scope of the invention.

EXAMPLES

Example 1: SMAR Scan® and MAR sequences

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A first rough evaluation of SMAR Scan® was done by analyzing experimentally defined human MARs and non-MAR sequences. As MAR sequences, the previous results from the analysis of human MARs from SMARt Db were used to plot a density histogram for each criterion as shown in Fig. 1. Similarly, non-MAR sequences were also analyzed and plotted. As non-MAR sequences, all Ref-Seq-contigs from the chromosome 22 were used, considering that this latter was big enough to contain a negligible part of MAR sequences regarding the part of non-MAR sequences.

The density distributions shown in Fig. 1 are all skewed with a long tail. For the highest bend, the highest major groove depth and the highest minor groove width, the distributions are right skewed. For the lowest melting temperature, the distributions are left-skewed which is natural given the inverse correspondence of this criterion regarding the three others. For the MAR sequences, biphasic distributions with a second weak peak, are actually apparent. And between MAR and non-MAR sequences distributions, a clear shift is also visible in each plot.

Among all human MAR sequences used, in average only about 70% of them have a value greater than the 75th quantile of human MARs distribution, this for the four different criteria. Similarly concerning the second weak peak of each human MARs distribution, only 15% of the human MAR sequences are responsible of these outlying values. Among these 15% of human MAR sequences, most are very well documented MARs, used to insulate transgene from position effects, such as the interferon locus MAR, the beta-globin locus MAR (Ramezani A, Hawley TS, Hawley RG, "Performance-and safety-enhanced lentiviral vectors containing the human interferon-beta scaffold attachment region and the chicken beta-globin insulator", Blood, 101:4717-4724, 2003), or the apolipoprotein MAR (Namciu, S, Blochinger KB, Fournier REK, "Human matrix attachment regions in-sulate transgene expression from chromosomal position effects in Drosophila melanogaster", Mol. Cell. Biol., 18:23 82-2391, 1998).

association between the four theoretical structural properties computed and the ATcontent. Fig. 2 represents the scatterplot and the corresponding correlation coefficient r for every pair of criteria.

Example 2: Distribution plots of MAR sequences by organism

MAR sequences from SMARt DB of other organisms were also retrieved and analyzed similarly as explained previously. The MAR sequences density distributions for the mouse, the chicken, the sorghum bicolor and the human are plotted jointly in Fig. 3.

45 Example 3: MAR prediction of the whole chromosome 22

All RefSeq contigs from the chromosome 22 were analyzed by SMAR Scan® using the default settings this time. The result is that SMAR Scan® predicted a total of 803 MARs, their average length being 446 bp, which means an average of one MAR predicted per 42 777 bp. The total length of the predicted MARs corresponds to 1% of the chromosome 22 length. The AT-content of the predicted regions ranged from

65,1% to 93.3%; the average AT-content of all these regions being 73.5%. Thus, predicted MARs were AT-rich, whereas chromosome 22 is not AT-rich (52.1% AT).

SMARTest was also used to analyze the whole chromosome 22 and obtained 1387 MAR candidates, their average length being 494 bp representing an average of one MAR predicted per 24 765 bp. The total length of the predicted MARs corresponds to 2% of the chromosome 22. Between all MARs predicted by the two softwares, 154 predicted MARs are found by both programs, which represents respectively 19% and 11% of SMAR Scan® and SMARTest predicted MARs. Given predicted MARs mean length for SMAR Scan® and SMARTest, the probability to have by chance an overlapping between SMAR Scan® and SMARTest predictions is 0.0027% per prediction.

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To evaluate the specificity of SMAR Scan® predictions, SMAR Scan® analyses were 15 performed on randomly shuffled sequences of the chromosome 22 (Fig. 4). Shuffled sequences were generated using 4 different methods; by a segmentation of the chromosome 22 into nonoverlapping windows of 10 bp and by separately shuffling the nucleotides in each window; by "scrambling" which means a permutation of all nucleotides of the chromosome: by "rubbling" which means a segmentation of the chro-20 mosome in fragments of 10 bp and a random assembling of these fragments and finally by order 1 Markov chains, the different states being the all the different DNA dinucleotides and the transition probabilities between these states being based on the chromosome 22 scan. For each shuffling method, five shuffled chromosome 22 were generated and analyzed by SMAR Scan® using the default settings. Concerning the 25 number hits, an average of 3 519 170 hits (sd: 18 353) was found for the permutated chromosome 22 within nonoverlapping windows of 10 bp. 171 936.4 hits (sd: 2 859.04) for the scrambled sequences and 24 708.2 hits (sd: 1 191.59) for the rubbled chromosome 22 and 2 282 hits in average (sd: 334.7) for the chromosomes generated according to order 1 Markov chains models of the chromosome 22, which respectively 30 represents 185% (sd: 0.5% of the mean), 9% (sd: 1.5%), 1% (sd: 5%) and 0.1% (sd: 15%) of the number of hits found with the native chromosome 22. For the number of MARs predicted, which thus means contiguous hits of length greater than 300, 1 997 MARs were predicted with the shuffled chromosome 22 within windows of 10 bp (sd: 31.2), only 2.4 MARs candidates were found in scrambled sequences (sd: 0.96) and 35 none for the rubbled and for the sequences generated according to Markov chains model, which respectively represents 249% and less than 0.3% of the number of predicted MARs found with the native chromosome 22. These data provide indications that SMAR Scan® detects specific DNA elements which organization is lost when the DNA sequences are shuffled.

Example 4: Analysis of known matrix attachment regions in the Interferon locus with SMAR Scan®

45 The relevance of MAR prediction by SMAR Scan® was investigated by analyzing the recently published MAR regions of the human interferon gene cluster on the short arm of chromosome 9 (9p.22). Goetze et al. (already cited) reported an exhaustive analysis of the WP18A10A7 locus to analyze the suspected correlation between BURs (termed in this case stress-induced duplex destabilization or SIDD) and in vitro binding to the nuclear matrix (Fig. 9, lower part). Three of the SIDD peaks were in agreement with the in vitro binding assay, while others did not match matrix attachment sites. Inspection of the interferon locus with SMAR Scan® (Fig. 9, top part) indicated that three majors peaks accompanied by clusters of SATB1, NMP4 and MEF2 regulators binding sites

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correlated well with the active MARs. Therefore, we conclude that the occurrence of predicted CUEs and binding sites for these transcription factors is not restricted to the cLysMAR but may be a general property of all MARs. These results also imply that the SMAR Scan® program efficiently detects MAR elements from genomic sequences.

Example 5: Accuracy of SMAR Scan® prediction and comparison with other predictive tools

The accuracy of SMAR Scan® was evaluated using six genomic sequences for which experimentally determined MARs have been mapped. In order to perform a comparison with other predictive tools, the sequences analyzed are the same with the sequences previously used to compare MAR-Finder and SMARTest. These genomic sequences are three plant and three human sequences (Table 1) totalizing 310 151 bp and 37 experimentally defined MARs. The results for SMARTest and MAR-Finder in Table 1 come from a previous comparison (Frisch M, Frech K, Klingenhoff A, Cartharius K, 15 Liebich I and Werner T, In silico pre-diction of scaffold/matrix attachment regions in large genomic sequences, Genome Research, 12:349-354, 2001.). MAR-Finder has been used with the default parameters excepted for the threshold that has been set to 0.4 and for the analysis of the protamine locus, the AT-richness rule has been excluded (to detect the non AT-rich MARs as was done for the protamine 20 locus).

Sequence, description and reference	Length	Experiment- ally defined MARs positions	SMARTest prediction positions	MAR-Finder prediction positions	SMAR Scan prediction positions
	(kb)	(kb)	(kb)	(kb)	(kb)
Cryza Sativa putative ADP-glucose pyro- phosphorylase subunit SH2 and putative NADPH dependant reductase A1 genes (U70541), [4]	30.034	0.0-1.2 5.4-7.4 17.3-18.5 20.0-23.1	6.5-7.0 15.2-15.7 16.2-16.6 17.6-18.3 19.6-20.1 20.7-21.3 23.6-23.9 25.0-25.4 27.5-27.9	15.7-15.9 17.5-18.4 19.8-20.4 21.3-21.5 23.9-24.2 24.7-25.1	15.6-16 17.6-18.2 21.6-22 23.4-23.8
Sorghum bicolor ADP- glucose pyrophopho- rylase subunit SH2, NADPH-dependant reducatse A1-b genes (AF010283), [4]	42.446	0.0-1.5 7.1-9.7 22.4-24.7 32.5-33.7 41.6-42.3	21.3-21.9 22.9-24.0 27.3-27.6	23.2-24.2 26.9-27.5	7,4-7.7 21,5-21,8 22,9-23,2 23,6-24,0 27,3-27,6 33,4-33,9
Sorghum bicolor BAC clone 110K5 (AF124045), [37]	78.195	~0.9 ~5.8 ~6.3 ~9.3 ~15.0 ~18.5 ~21.9 ~23.3 ~25.6 ~44.1 ~48.5 ~57.9 ~62.9 ~67.1 ~69.3 ~73.7	15.1-15.8 21.7-22.0 - - - 44.1-44.5 47.9-49.5 - - 63.1-63.7 - 74.3-74.7	47.9-49.4	21.4-21.9 29.2-29.5 39.0-40.0 48.1-48.6 48.8-49.3
Human alpha-1-antitry- sin and corticosteroid binding globulin intergenic region (AF 156545), [35]	30.461	2.6-6.3 22.0-30.4	5.5-6.0 25.7-26.2 27.5-27.8	3.0-3.2 5.1-6.0 24.9-25.3 25.5-25.8 26.2-26.4 27.5-28.2	5,4-5.8 - 25.8-26.4
Human protamine locus (U15422). [24]	53.060 75.955	8.8-9.7 32.6-33.6 37.2-39.4 51.8-53.0	-	8.0-8.9* 33.9-34.8* 33.9-34.8*	2.3-2.6
Human beta-globin locus (U01317), [21]	10,900	15.6-19.0 44.7-52.7	18.0-18.4 34.4-34.9	15.5-16.0 18.0-18.4 50.6-50.8	2.3-2.6 15.3-15.6 - -
		60.0-70.0	56.6-57.1 59.8-60.3 65.6-66.0	56,5-57,2 58,1-58,5 63,0-63,6	62.8-63.1

Sum(kb)	310.151	at least 56.1	67.6-67.9 68.8-69.1 14.5	68.7-69.3	66.3-66.7 - 9.5
Total numbers: Average kb /predicted MAR True positives (number of experimentally defined MAR found) False positives False negatives Specificity Sensitivity		37	28 11.076 19[14] 9 23 19/28= 68% 14/37= 38%	25 12.406 20[12] 5 25 20/25= 80% 12/37= 32%	22 14.097 17[14] 5 23 17/22= 77% 14/37= 38%

Table 1: Evaluation of SMAR Scan® accuracy

Six different genomic sequences, three plant and three human sequences, for which experimentally defined MARs are known, were analyzed with MAR-Finder, SMARTest and SMAR Scan®. True positive matches are printed in bold, minus (-) indicates less enegative matches. Some of the longer experimentally defined MARs contained more than one in silico prediction, each of them was counted as true positive match.
 Therefore, the number of true in silico predictions is higher than the number of experimentally defined MARs found. Specificity is defined as the ratio of true positive predictions, whereas sensitivity is defined as the ratio of experimentally defined MARs

found, * AT-rich rule excluded using MAR-Finder.

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- SMARTest predicted 28 regions as MARs, 19 (true positives) of these correlate with experimentally defined MARs (specificity: 68%) whereas 9 (32%) are located in non-MARs (false positives). As some of the longest experimentally determined MARs contains more than one in silico prediction, the 19 true positives correspond actually to 14 different experimentally defined MARs (sensitivity: 38%). MARFinder predicted 25 regions as MARs, 20 (specificity: 80%) of these correlate with experimentally defined MARs (sensitivity: 32%). SMAR Scan® predicted 22 regions, 17 being true positives
- 25 As another example, the same analysis has been applied to human chromosomes 1 and 2 and lead to the determination of 23 MARs sequences (SEQ ID N° 1 to 23). These sequences are listed in Annex 1 in ST25 format.

(specificity: 77%) matching 14 different experimentally defined MARs (sensitivity: 38%).

Example 6: Analyses of the whole genome using the combined method (SMAR Scan®-pfsearch)

In order to test the potential correlation between the structural features computed by SMAR Scan® and the S/MAR functional activity, the whole human genome has been analyzed with the combined method with very stringent parameters, in order to get sequences with the highest values for the theoretical structural features computed, which are called "super" S/MARs below. This was done with the hope to obtain predicted MAR elements with a very potential to increase transgene expression and recombinant protein production. The putative S/MARs hence harvested were first analyzed from the bioinformatics perpective in an attempt to characterize and classify the

6.1 S/MARs predicted from the analysis of the whole human genome

As whole human genome sequence, all human RefSeq (National Center for Biotechnology Information, The NCBI handbook [Internet]. Bethesda (MD): National Library of Medicine (US), Oct. Chapter 17, The Reference Sequence (RefSeq) Project, 2002 (Available from http://www.ncbi.nih.gov/entrez/query.fcgi?db=Books) contigs (release 5) were used and analyzed with the combined method, using SMAR Scan® as filter in the first level processing, employing default settings except for the highest bend cutoff value, whereas a stringent threshold of 4.0 degrees (instead of 3.202 degrees) has been used for the DNA bending criterion.

In the second level processing, predicted transcription factors binding have been sought in the sequences selected from the previous step without doing any filtering on these sequences.

The analysis by the combined method of the whole human genome came up with a total of 1757 putative "super" S/MARs representing a total of 1065 305 bp (0.35% of the whole human genome). Table 2 shows for each chromosome: its size, its number of genes, its number of S/MARs predicted, its S/MARs density per gene and its kb per S/MAR. This table shows that there are very various gene densities per S/MAR predicted for the different chromosomes (standard devlation represents more than 50% of the mean of the density of genes per S/MAR predicted and the fold difference between the higher and the lower density of genes per S/MAR is 6,5). Table 2 also shows that the kb per S/MAR varies less that the density of genes per S/MAR (standard deviation represents 25% of the mean of kb per S/MAR and the fold difference between the higher and the lower kb per S/MAR is 3.2).

Chromosome	Number of genes per chromosome	Size of the chromosome (millions bp)	Number of S/MARs predicted	Density of genes per S/MAR	Kb per S/MAR
1	2544	230	85	29.9	2705
2	1772	241	143	12.3	1685
3	1406	198	101	13.9	1960
4	1036	190	118	8.7	1610
5	1233	180	116	10.6	1551
6	1247	170	94	13.2	1808
7	1383	160	179	7.7	1754
8	942	145	77	12.2	1883
9	1100	119	48	22.9	2479
10	1003	133	71	14.1	1873
11	1692	132	67	25.2	1970
12	1278	131	78	16,3	1679
13	506	97	70	7.2	1385
14	1168	88	36	32.4	2444
15	895	83	35	25.5	2371
16	1107	81	41	27	1975
17	1421	80	37	38.4	2162
18	396	75	51	7.7	1470
19	1621	56	36	45.02	1555
20	724	60	28	25.8	2142
21	355	34	18	19.7	1888
22	707	34	28	25.2	1214
x	1168	154	170	6.8	905
Y	251	25	30	8.3	833
Sum	26 955	3 050	1 757	457	433 12
Mean	1 123	127	73	19	1 804
Sd	510	72.8	45	10	462

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corresponds to the NCBI human genome statistics (Build 34 Version 3) (National Center for Biotechnology Information, The NCBI handbook [Internet]. Bethesda (MD): National Library of Medicine (US), Oct. Chapter 17, The Reference Sequence (RefSeq) Project, 2002 (Available from http://www.ncbi.nih.gov/entrez/query.fcgi?db=Books) based on GenBank annotations. Chromosome sizes are the sum of the corresponding human RefSeq (National Center for Biotechnology Information, The NCBI handbook [Internet]. Bethesda (MD): National Library of Medicine (US), Oct. Chapter 17, The Reference Sequence (RefSeq) Project, 2002 (Available from http://www.ncbi.nih.gov/entrez/query.fcgi?db=Books) (release 5) contig lengths

10 6.2 Bioinformatics analysis of "super" MARS for transcription factor binding sites

The 1757 predicted "super" S/MARs sequences obtained previously by SMAR Scan® were then analyzed for potential transcription factors binding sites. This has been achieved using RMatch MP Professional (Kel AE, Gossling E, Reuter I, Cheremushkin E, KelMargoulis OV, Wingender E, MATCH: A tool for searching transcription factor binding sites in DNA sequences, Nucleic Acids Res. 31(13):35769, 2003), a weight matrixbased tool based on TRANSFAC (Wingender E, Chen X, Fricke E, Geffers R, Hehl R, Liebich I, Krull M, Matys V, Michael H, Ohnhauser R, Pruss M, Schacherer F, Thiele S, Urbach S, The TRANSFAC system on gene expression regulation, Nucleic Acids Research , 29(1):2813, 2001). Match 2.0 Professional has been used with most of the default settings Match analysis was based on TRANSFAC Professional, release 8.2 (20040630). The sums of all transcription factors binding prediction on the 1757 sequences analyzed according to Match are in Table 3. Based on this table, only the transcription factors totalizing at least 20 hits over the 1757 sequences analyzed were considered for further analyses.

Hereafter are some of the human transcription factors that are the most often predicted to bind on the 1757 putative S/MAR sequences and their Match description: Cdc5 (cell division control protein 5) a transcriptional regulator/repressor, Nkx3A a homeodomain protein regulated by androgen, POU1F1 (pituitaryspecific positive transcription factor 1) which is specific to the pituitary and stimulates cells proliferation. Thus, in addition to SATB1, NMP4 and MEF2, other transcription factors can participate in the activity of MARs.

AP1	1	AR	2	Bach2	1	Brn2	1
C/EBP	20	C/EBPgamma	5	CDP CR3	1	COMP1	2
CREBP1	34	Cdc5	858	Cdx2	35	Evi1	472
FOX	78	FOXD3	79	FOXJ2	244	FOXP3	29
Freac7	272	GATA1	2	GATA3	142	GATA4	125
HFH1	12	HFH3	1	HLF	275	HNF1	337
HNF3alpha	23	HNF3beta	71	HP1	2	Lhx3	22
MEF2	114	MRF2	57	Myc	18	NKX3A	849
Nkx25	2	Oct1	191	PBX	5	POU1F1	483
POU3F2	11	POU6F1	29	Pax3	3	Pax6	20
Pit1	505	SRF	8	TEF	2852	TFIIA	14
TTF1	1	V\$MTATA_B	4	VBP	53	Vmw65	1
XFD1	65	XFD2	418	XFD3	2		

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Table 3 is a summary of all transcription factors binding prediction (totalizing 20 hits or more) on the 1757 sequences analyzed.

5 6.3 Bioinformatics analysis of predicted "super" MARs for dinucleotide frequencies

Various computer analysis were performed in order to easily identify "super" S/MAR sequences using an explicit criterion that could be identified without computing. Among those, a di-nucleotide analysis was performed on the 1757 superMARs, computing each of the 16 possible dinucleotide percentage for each sequence considering both strands in the 5' > 3' direction.

A summary (min., max., median, mean, 25th percentile and 75th percentile) as well as the histograms of each dinucleotide percentage over the 1757 S/MAR sequences are respectively presented in Table 4. A similar analysis was performed on randomly selected sequences from the human genome, representing randomly selected non-S/MAR sequences (which might however contain some MARs). Table 5 represents respectively a summary of the dinucleotide content analysis for these sequences.

Table 4: Dinucleotide percentages over the 1757 S/MAR sequences

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	AA %	AC %	AG %	AT %
Minimum	0.000	0.0000	0.0000	18.50
25th percentile	4.234	0.9372	0.1408	32.11
Median	7.843	2,2408	0.4777	34.68
Mean	7.184	3.2117	1.0865	34.32
75th percentile	10.110	4.7718	1.5096	36.94
Maximum	17.290	12.9479	8.1230	50.00
	CA %	CC %	CG %	CT %
Minimum	0.0000	0.00000	0.0000	0.0000
25th percentile	0.9695	0.00000	0.0000	0.1408
Median	1.9776	0.00000	0.0000	0.4777
Mean	2.6977	0.14123	0.2709	1.0865
75th percentile	3.7543	0.09422	0.1256	1.5096
Maximum	10.4061	4.24837	7.4410	8,1230
	GA %	GC %	GG %	GT %
Minimum	0,00000	0.0000	0.00000	0.0000
25th percentile	0.08696	0.0000	0.00000	0.9372
Median	0.32616	0.0000	0.00000	2.2408
Mean	0.63347	0.2104	0.14123	3.2117
75th percentile	0.83333	0.1914	0.09422	4.7718
Maximum	5.77889	9.8795	4.24837	12.9479
	TA %	TC %	TG %	TT %
Minimum	28.63	0.00000	0.0000	0.000
25th percentile	33.48	0.08696	0.9695	4.234
Median	35.22	0.32616	1.9776	7.843
Mean	35.29	0.63347	2.6977	7.184
75th percentile	37.14	0.83333	3.7543	10.110
Maximum	50.00	5.77889	10.4061	17.290

Considering the results of the predicted S/MAR elements and of the nonS/MAR sequences in the summary tables, noticeable differences can be noticed in the AT et TA dinucleotide contents between these two groups of sequences. AT and TA represent respectively at least 18,5 % and 28.6 % of the dinucleotide content of the predicted S/MAR sequences, whereas the minimum percentages for the same dinucleotides in

nonS/MAR sequences are respectively 0.3 % and 0%. Similarly, the maximum CC and GG content in S/MAR sequences is 4.2 %, whereas in nonS/MAR sequences the percentages for these two dinucleotides can amount up to 20.8 %.

The correlation between AT and TA dinuclectide percentages and the DNA highest bend as computed by SMAR Scan® is depicted in Fig. 17 for the predicted S/MAR sequences and in Fig. 18 for the nonS/MAR sequences. The different scatterplots of these figures show that the TA percentage correlates well with the predicted DNA bend as predicted by SMAR Scan®.

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Table 5: Dinucleotide percentages over the 1757 nonS/MAR sequences summary

	AA %	AC %	AG %	AT %
Minimum	0.000	1.735	1.512	0.3257
25th percentile	7.096	4.586	6.466	5.1033
Median	9.106	5.016	7.279	6.8695
Mean	8.976	5.054	7.184	7.0108
75th percentile	10.939	5,494	7.969	8.7913
Maximum	17.922	13.816	12.232	23.1788
	CA%	CC %	CG %	CT %
Minimum	3.571	0.8278	0.0000	1.512
25th percentile	6.765	4.1077	0.4727	6.466
Median	7.410	5.5556	0.8439	7.279
Mean	7.411	5.9088	1.2707	7.184
75th percentile	8.010	7.2460	1.5760	7.969
Maximum	15.714	20.8415	12.6074	12.232
	GA %	GC %	GG %	GT %
Minimum	1.319	0.4967	0.8278	1.735
25th percentile	5.495	3.2615	4.1077	4,586
Median	6.032	4.4092	5.5556	5.016
Mean	6.065	4.7468	5.9088	5.054
75th percentile	6.602	5.8824	7.2460	5.494
Maximum	10.423	16.0000	20.8415	13.816
	TA %	TC %	TG %	TT %
Minimum	0.000	1.319	3.571	0.000
25th percentile	3.876	5.495	6.765	7.096
Median	5.625	6.032	7.410	9.106
Mean	5.774	6.065	7.411	8.976
75th percentile	7.464	6.602	8.010	10.939
Maximum	24 338	10.423	15 714	17 922

Four of the novel super MARs were randomly picked and analyzed for AT and TA dinucleotide content, and compared with the previously known chicken lysMAR, considering windows of 100 base pairs (Table 6).

Surprinsigly, Applicants have shown that all of the super MARs have AT dinucleotide frequencies greater then 12%, and TA dinucleotides greater than 10% of the total dinucleotides analysed in a window of 100base pairs of DNA. The most efficient MARs display values around 34% of the two dinucleotide pairs.

Table 6. Summary of %AT and TA dinucleotide frequencies of experimentally verified MARs

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CLysMAR (average of CUEs)	AT%: 12.03	TA%: 10.29	SEQ ID No
P1 68	AT%: 33.78	TA%: 33.93	SEQ ID No
P1 6	AT%: 34.67	TA%: 34.38	SEQ ID No

P1 42	AT%: 35.65	TA%: 35.52	SEQ ID No
Mean value for all human "super"MARs	AT%: 34.32	TA%: 35.29	
Mean value for all human non-MARs	AT%: 7.01	TA%: 5.77	

6.4 Analysis of orthologous intergenic regions of human and mouse genomes

- In order to get an insight on S/MAR evolution, orthologous intergenic regions of human and mouse genomes have been analysed with SMAR Scan®. The data set used is composed of 87 pairs of complete orthologous intergenic regions from the human and mouse genomes (Shabalina SA, Ogurtsov AY, Kondrashov VA, Kondrashov AS, Selective constraint in intergenic regions of human and mouse genomes, *Trends* Genet, 17(7):3736, 2001) (average length ~12 000 bp) located on 12 human and on 12 mouse chromosomes, the synteny of these sequences was confirmed by pairwise sequence alignment and consideration of the annotations of the flanking genes (experimental or predicted).
- 15 Analysis of the 87 human and mouse orthologous intergenic sequences have been analysed with SMAR Scan® using its default settings. Analysis of the human sequences yielded a total of 12 S/MARs predicted (representing a total length of 4 750 bp), located on 5 different intergenic sequences.
- Among the three human intergenic sequences predicted to contain a "super" S/MAR 20 using SMAR Scan® stringent settings, one of the corresponding mouse orthologous intergenic sequence is also predicted to contain a S/MAR (human EMBL ID: Z96050, position 28 010 to 76 951 othologous to mouse EMBL ID: AC015932, positions 59 884 to 89 963). When a local alignement of these two orthologous intergenic sequences is 25 performed, the best local alignement of these two big regions correspond to the regions predicted by SMAR Scan® to be S/MAR element. A manual search for the mouse orthologs of the two other human intergenic sequences predicted to contain a "super" S/MAR was performed using the Ensembl Genome Browser (http://ensembl.org). The mouse orthologous intergenic sequences of these two human sequences were 30 retrieved using Ensembl orthologue predictions (based on gene names), searching the orthologous mouse genes for the pairs of human genes flanking these intergenic regions.
- Because SMAR Scan® has been tuned for human sequences and consequently yields little "super"MARs with mouse genomic sequences, its default cutoff values were slightly relaxed for the minimum size of contiguous hits to be considered as S/MAR (using 200 bp instead of 300 bp). Analysis by SMAR Scan® of these mouse sequences predicted several S/MARs having high values for the different computed structural features. This finding suggests that the human MAR elements are conserved across species.

Example 7: Dissection of the chicken lysozyme gene 5'- MAR

The 3000 base pair 5¹-MAR was dissected into smaller fragments that were monitored for effect on transgene expression in Chinese hamster ovary (CHO) cells. To do so, seven fragments of ~400 bp were generated by polymerase chain reaction (PCR). These PCR-amplified fragments were contiguous and cover the entire MAR sequence when placed end-to-end. Four copies of each of these fragments were ligated in a head-to-tail orientation, to obtain a length corresponding to approximately half of that of

the natural MAR. The tetramers were inserted upstream of the SV40 promoter in pGEGFPControl, a modified version of the pGL3Control vector (Promega). The plasmid pGEGFPControl was created by exchanging the luciferase gene of pGL3Control for the EGFP gene from pEGFP-N1 (Clontech). The 5'-MAR-fragment-containing plasmids thus created were co-transfected with the resistance plasmid pSVneo in CHO-DG44 cells using LipofectAmine 2000 (Invitrogen) as transfection reagent, as performed previously (Zahn-Zabal, M., et al., "Development of stable cell lines for production or regulated expression using matrix attachment regions" *J Biotechnol*, 2001. 87(1): p. 29-42.). After selection of the antibiotic (G-418) resistant cells, polyclonal cell populations were analyzed by FACS for EGFP fluorescence.

Transgene expression was expressed at the percentile of high expressor cells, defined as the cells which fluorescence levels are at least 4 orders of magnitude higher than the average fluorescence of cells transfected with the pGEGFPControl vector without MAR. Fig. 5 shows that multimerized fragments B, K and F enhance transgene expression, despite their shorter size as compared to the original MAR sequence. In contrast, other fragments are poorly active or fully inactive.

Example 8: Specificity of B, K and F regions in the MAR context

The 5'-MAR was serially deleted from the 5'-end (Fig.6, upper part) or the 3'-end (Fig.6, lower part), respectively. The effect of the truncated elements was monitored in an assay similar to that described in the previous section. Figure 6 shows that the loss of ability to stimulate transcene expression in CHO cells was not evenly distributed.

In this deletion study, the loss of MAR activity coincided with discrete regions of transition which overlap with the 5'-MAR B-, K- and F-fragment, respectively. In 5' deletions, activity was mostly lost when fragment K and F were removed. 3' deletions that removed the F and b elements had the most pronounced effects. In contrast, flanking regions A, D, E and G that have little or no ability to stimulate transgene expression on their own (Fig. 5), correspondingly did not contribute to the MAR activity in the 5'- and 3'-end deletion studies (Fig. 6).

Example 9:Structure of the F element

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The 465 bp F fragment was further dissected into smaller sub-fragments of 234, 243, 213 bp and 122, 125 and 121 bp, respectively. Fragments of the former group were octamerized (8 copies) in a head-to-tail orientation, while those of the latter group were similarly hexa-decamerized (16 copies), to maintain a constant length of MAR sequence. These elements were cloned in pGEGFPControl vector and their effects were assayed in CHO cells as described previously. Interestingly, fragment FIII retained most of the activity of the full-length F fragment whereas fragment FII, which contains the right-hand side part of fragment FIII, lost all the ability to stimulate transgene expression (Fig. 7). This points to an active region comprised between nt 132 and nt 221 in the FIB fragment. Consistently, multiple copies of fragments FI and FIB, which encompass this region, displayed similar activity. FII on its own has no activity. However, when added to FIB, resulting in FIII, it enhances the activity of the former. Therefore FIIA appears to contain an auxiliary sequence that has little activity on its own, but that strengthens the activity of the minimal domain located in FIB.

Analysis of the distribution of individual motifs within the lysozyme gene 5'-MAR is shown in Fig. 8 A, along with some additional motifs that we added to the analysis. Most of these motifs were found to be dispersed throughout the MAR element, and not

specifically associated with the active portions. For instance, the binding sites of transcription factors and other motifs that have been associated with MARs were not preferentially localized in the active regions. It has also been proposed that active MAR sequences may consist of combination of distinct motifs. Several computer programs (MAR Finder, SMARTest, SIDD duplex stability) have been reported to identify MARs as regions of DNA that associate with the DNA matrix. They are usually based on algorithms that utilizes a predefined series of sequence-specific patterns that have previously been suggested as containing MAR activity, as exemplified by MAR Finder, now known as MAR Wiz. The output of these programs did not correlate well with the 10 transcriptionally active portions of the cLysMAR. For instance, peaks of activity obtained with MAR Finder did not clearly match active MAR sub-portion, as for instance the B fragment is quite active in vivo but scores negative with MAR Finder (Fig. 8B. compare the top and middle panels). Bent DNA structures, as predicted by this program, did not correlate well either with activity (Fig. 8B, compare the top and bottom panels). Similar results were obtained with the other available programs (data not shown).

The motifs identified by available MAR prediction computer methods are therefore unlikely to be the main determinants of the ability of the cLvsMAR to increase gene expression. Therefore, a number of other computer tools were tested. Surprisingly, predicted nucleosome binding sequences and nucleosome disfavouring sequences were found to be arranged in repetitively interspersed clusters over the MAR, with the nucleosome favouring sites overlapping the active B, K and F regions. Nucleosome positioning sequences were proposed to consist of DNA stretches that can easily wrap around the nucleosomal histones, and they had not been previously associated with MAR sequences.

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Nucleosome-favouring sequences may be modelled by a collection of DNA features that include moderately repeated sequences and other physico-chemical parameters that may allow the correct phasing and orientation of the DNA over the curved histone 30 surface, Identification of many of these DNA properties may be computerized, and up to 38 different such properties have been used to predict potential nucleosome positions. Therefore, we set up to determine if specific components of nucleosome prediction programs might correlate with MAR activity, with the objective to construct a tool allowing the identification of novel and possibly more potent MARs from genomic sequences.

To determine whether any aspects of DNA primary sequence might distinguish the active B. K and F regions from the surrounding MAR sequence, we analyzed the 5'-MAR with MAR Scan®. Of the 38 nucleosomal array prediction tools, three were found 40 to correlate with the location of the active MAR sub-domains (Fig. 9A), Location of the MAR B. K and F regions coincides with maxima for DNA bending, major groove depth and minor groove width. A weaker correlation was also noted with minima of the DNA melting temperature, as determined by the GC content. Refined mapping over the MAR F fragment indicated that the melting temperature valley and DNA bending summit 45 indeed correspond the FIB sub-fragment that contains the MAR minimal domain (Fig. 9B). Thus active MAR portions may correspond to regions predicted as curved DNA regions by this program, and we will refer to these regions as CUE-B, CUE-K and CUE-F in the text below. Nevertheless, whether these regions correspond to actual bent DNA and base-pair unwinding regions is unknown, as they do not correspond to bent DNA 50 as predicted by MAR Wiz (Fig.9B).

Example 10: Imprints of other regulatory elements in the F fragment

Nucleosome positioning features may be considered as one of the many specific chromatin codes contained in genomic DNA. Although this particular code may contribute to the activity of the F region, it is unlikely to determine MAR activity alone, as the 3' part of the F region enhanced activity of the minimal MAR domain contained in the FIB portion. Using the MatInspector program (Genomatix), we searched for transcription factor binding sites with scores higher than 0.92 and found DNA binding sequences for the NMP4 and MEF2 proteins in the 3' part of the F fragment (Fig. 8B). To determine whether any of these transcription factor-binding sites might localize close to the B and K active regions, the entire 5'-MAR sequence was analyzed for binding by NMP4 and MEF2 and proteins reported to bind to single-stranded or double-stranded form of BURs. Among those, SATB1 (special AT-rich binding protein 1) belongs to a class of DNA-binding transcription factor that can either activate or repress the expression of nearby genes. This study indicated that specific proteins such as SATB1. NMP4 (nuclear matrix protein 4) and MEF2 (myogenic enhancer factor 2), have a 15 - specific distribution and form a framework around the minimal MAR domains of cLysMAR (Fig. 10). The occurrence of several of these NMP4 and SATB1 binding sites has been confirmed experimentally by the EMSA analysis of purified recombinant proteins (data not shown).

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Example 11: Construction of artificial MARs by combining defined genetic 20 elements

To further assess the relative roles of the various MAR components, the cLysMAR was deleted of all three CUE regions (Fig. 11, middle part), which resulted in the loss of part of its activity when compared to the complete MAR sequence similarly assembled from all of its components as a control (Fig. 11, top part). Consistently, one copy of each CUE alone, or one copy of each of the three CUEs assembled head-to-tail, had little activity in the absence of the flanking sequences. These results strengthen the conclusion that optimal transcriptional activity requires the combination of CUEs with of flanking sequences. Interestingly, the complete MAR sequence generated from each of its components, but containing also BgIII-BamHI linker sequences (AGATCC) used to assemble each DNA fragment, displayed high transcriptional activity (6 fold activation) as compared to the 4.8 fold noted for the original MAR element in this series of assays (see Fig. 5).

35 We next investigated whether the potentially curved DNA regions may also be active in an environment different from that found in their natural MAR context. Therefore, we set up to swap the CUE-F, CUE-B and CUE-K elements, keeping the flanking sequences unchanged. The sequences flanking the CUE-F element were amplified by PCR and assembled to bracket the various CUEs, keeping their original orientation and distance, 40 or without a CUE. These engineered ~1.8 kb MARs were then assayed for their ability to enhance transgene expression as above. All three CUE were active in this context, and therefore there action is not restricted to one given set of flanking sequences. Interestingly, the CUE-K element was even more active than CUE-F when inserted between the CUE-F flanking sequences, and the former composite construct exhibited 45 an activity as high as that observed for the complete natural MAR (4.8 fold activation). What distinguishes the CUE-K element from CUE-F and CUE-B is the presence of overlapping binding sites for the MEF-2 and SatB1 proteins, in addition to its CUE feature. Therefore, fusing CUE-B with CUE-F-flanking domain results in a higher 50 density of all three binding sites, which is likely explanation to the increased activity. These results indicate that assemblies of CUEs with sequences containing binding sites

for proteins such as NMP4, MEF-2, SatB1, and/or polyPpolyQ proteins constitute potent artificial MAR sequences.

Example 12 : Expression vectors

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Three expression vectors according to the present invention are represented on Figure 12.

Plasmid pPAG01 is a 5640 bp pUC19 derivative. It contains a 2960 bp chicken DNA fragment cloned in *BamH1* and *Xbal* restriction sites. The insert comes from the border of the 5'-end of the chicken lyzozyme locus and has a high A/T-content.

Plasmid pGEGFP (also named pSV40EGFP) control is a derivative of the pGL3-control vector (Promega) in which the luciferase gene sequence has been replaced by the EGFP gene sequence form the pEGFP-N1 vector (Clontech). The size of pGEGFP plasmid is 4334bp.

Plasmid pUbCEGFP control is a derivative of the pGL3 wit an Ubiquitin promoter.

Plasmid pPAG01GFP (also named pMAR-SV40EGFP) is a derivative of pGEGFP with the 5'-Lys MAR element cloned in the MCS located just upstream of the SV40 promoter. The size of the pPAG01EGF plasmid is 7285bp.

Example 13: Effect of the additional transfection of primary transfectant cells on transgene expression

- One day before transfection, cells were plated in a 24-well plate, in growth medium at a density of 1.35 x 10⁵ cells/well for CHO-DG44 cells. 16 hours post-inoculum, cells were transfected when they reached 30-40% confluence, using Lipofect-AMINE 2000 (hereinafter LF2000), according to the manufacturer's instructions (Invitrogen). Twenty-seven microliters of serum free medium (Opti-MEM; Invitrogen) containing 14 µl of
 LF2000 were mixed with 27 µl of Opti-MEM containing 830 ng of linear plasmid DNA. The antibiotic selection plasmid (pSVneo) amounted to one tenth of the reporter plasmid bearing the GFP transgene. The mix was incubated at room temperature for 20
- min, to allow the DNA-LF2000 complexes to form. The mixture was diluted with 300 µl of Opti-MEM and poured into previously emptied cell-containing wells. Following 3 hours incubation of the cells with the DNA mix at 37°C in a CO₂ incubator, one ml of DMEM-based medium was added to each well. The cells were further incubated for 24 hours in a CO₂ incubator at 37°C. The cells were then transfected a second time according to the method described above, except that the resistance plasmid carried
- another resistance gene (pSVpuro). Twenty-four hours after the second transfection, 40 cells were passaged and expanded into a T-75 flask containing selection medium supplemented with 500 µg/ml G-418 and 5 µg/ml puromycin. After a two week selection period, stably transfected cells were cultured in 6-well plates. Alternatively, the cell population was transfected again using the same method, but pTKhygro (Clontech) and pSVdhfr as resistance plasmids. The expression of GFP was analysed with
- 45 Fluorescence-activated cell sorter (FACS) and with a Fluoroscan.

Fig.13 shows that the phenotype of the twice-transfected cells (hereafter called secondary transfectants) not only was strongly coloured, such that special bulb and filter were not required to visualize the green color from the GFP protein, but also contained a majority of producing cells (bottom right-hand side FACS histogram) as compared to the parental population (central histogram). This level of fluorescence corresponds to specific cellular productivities of at least 10 pg per cell per day. Indeed,

cells transfected only one time (primary transfectants) that did not express the marker protein were almost totally absent from the cell population after re-transfection. Bars below 10¹ units of GFP fluorescence amounted 30% in the central histogram and less than 5% in the right histogram. This suggested that additional cells had been 5 transfected and successfully expressed GFP.

Strikingly, the amount of fluorescence exhibited by re-transfected cells suggested that the subpopulation of cells having incorporated DNA twice expressed much more GFP than the expected two-fold increase. Indeed, the results shown in Table 2 indicate that the secondary transfectants exhibited, on average, more than the two-fold increase of GFP expected if two sets of sequences, one at each successive transfection, would have been integrated independently and with similar efficiencies. Interestingly, this was not dependent on the promoter sequence driving the reporter gene as both viral and cellular promoter-containing vectors gave a similar GFP enhancement (compare lane 1 and 2). However, the effect was particularly marked for the MAR-containing vector as compared to plasmids without MAR- (lane 3), where the two consecutive transfections resulted in a 5.3 and 4.6 fold increase in expression. In two distinct experiments.

Type of plasmids	Primary	Secondary	EGFP fluorescence	
	transfection	transfection	Fold increase	
pUbCEGFP	4'992	14'334	2.8	
pSV40EGFP	4'324	12'237	2.8	
pMAR-SV40EGFP	6'996	36'748	5.3	

Type of plasmids	Primary transfection	Secondary transfection	EGFP fluorescence Fold increase
pUbCEGFP	6'452	15'794	2.5
pSV40EGFP	4'433	11'735	2.6
pMAR-SV40EGFP	8'116	37'475	4.6

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Table 7. Effect of re-transfecting primary transfectants at 24 hours interval on GFP expression. Two independent experiments are shown. The resistance plasmid pSVneo was co-transfected with various GFP expression vectors. One day post-transfection, cells were re-transfected with the same plasmids with the difference that the resistance plasmid was changed for pSVpuro. Cells carrying both resistance genes were selected on 500 µg/ml G-418 and 5µg/ml purmycin and the expression of the reporter gene marker was quantified by Fluoroscan. The fold increases correspond to the ratio of fluorescence obtained from two consecutive transfections as compared to the sum of fluorescence obtained from the corresponding independent transfections. The fold increases that were judged significantly higher are shown in bold, and correspond to fluorescence values that are consistently over 2-fold higher than the addition of those obtained from the independent transfections.

35 The increase in the level of GFP expression in multiply transected cells was not expected from current knowledge, and this effect had not been observed previously.

Taken together, the data presented here support the idea that the plasmid sequences that primarily integrated into the host genome would facilitate integration of other plasmids by homologous recombination with the second incoming set of plasmid molecules. Plasmid recombination events occur within a 1-h interval after the plasmid DNA has reached the nucleus and the frequency of homologous recombination

between co-injected plasmid molecules in cultured mammalian cells has been shown to be extremely high, approaching unity (Folger, K.R., K. Thomas, and M.R. Capecchi, Nonreciprocal exchanges of information between DNA duplexes coinjected into mammalian cell nuclei. Mol Cell Biol, 1985. 5(1): p. 59-69], explaining the integration of multiple plasmid copies. However, homologous recombination between newly introduced DNA and its chromosomal homolog normally occurs very rarely, at a frequency of 1 in 10³ cells receiving DNA to the most [Thomas, K.R., K.R. Folger, and M.R. Capecchi, High frequency targeting of genes to specific sites in the mammalian genome. Cell, 1986. 44(3): p. 419-28.]. Thus, the results might indicate that the MAR element surprisingly acts to promote such recombination events. MARs would not only modify the organization of genes in vivo, and possibly also allow DNA replication in conjunction with viral DNA sequences, but they may also act as DNA recombination signals.

15 Example 14 : MARs mediate the unexpectedly high levels of expression in multiply transfected cells

If MAR-driven recombination events were to occur in the multiple transfections process, we expect that the synergy between the primary and secondary plasmid DNA would be affected by the presence of MAR elements at one or both of the transfection steps. We examined this possibility by multiply transfections of the cells with pMAR alone or in combination with various expression plasmids, using the method described previously. Table 3 shows that transfecting the cells twice with the pMAR-SV40EGFP plasmid gave the highest expression of GFP and the highest degree of enhancement of all conditions (4.3 fold). In contrast, transfecting twice the vector without MAR gave little or no enhancement, 2.8-fold, instead of the expected two-fold increase. We conclude that the presence of MAR elements at each transfection step is necessary to achieve the maximal protein synthesis.

Table 8

		Tubic 0			
Primary transfection		Secondary transfection			
Type of plasmid	EGFP-	Type of plasmid	EGFP-	Fold	
	fluorescence		fluorescence	increase	
pMAR	0	pMAR	0	0	
		pSV40EGFP	15'437	2.3-2.5	
		pMAR-SV40EGFP	30'488	2.6-2.7	
pMAR-SV40EGFP	11'278	pMAR-SV40EGFP	47'027	4.3-5.3	
		pMAR	12'319	1.0-1.1	
pSV40EGFP	6'114	pSV40EGFP	17'200	2.8	
		pMAR	11'169	1.8-2.3	

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Interestingly, when cells were first transfected with pMAR alone, and then retransfected with pSV40EGFP or pMAR-SV40EGFP, the GFP levels were more than doubled as compared to those resulting from the single transfection of the later plasmids (2.5 and 2.7 fold respectively, instead of the expected 1-fold). This indicates that the prior transfection of the MAR can increase the expression of the plasmid used in the second transfection procedure. Because MARs act only locally on chromatin structure and gene expression, this implies that the two types of DNA may have integrated at a similar chromosomal locus. In contrast, transfecting the GFP expression vectors alone, followed by the MAR element in the second step, yielded little or no improvement of the GFP levels. This indicates that the order of plasmid

transfection is important, and that the first transfection event should contain a MAR element to allow significantly higher levels of transgene expression.

If MAR elements favoured the homologous recombination of the plasmids remaining in episomal forms from the first and second transfection procedures, followed by their cointegration at one chromosomal locus, one would expect that the order of plasmid transfection would not affect GFP levels. However, the above findings indicate that it is more favourable to transfect the MAR element in the first rather than in the second transfection event. This suggests the following molecular mechanism: during the first transfection procedure, the MAR elements may concatemerize and integrate, at least in part, in the cellular chromosome. This integrated MAR DNA may in turn favour the further integration of more plasmids, during the second transfection procedure, at the same or at a nearby chromosomal locus.

15 Example 15: MARs as long term DNA transfer facilitators

If integrated MARs mediated a persistent recombination-permissive chromosomal structure, one would expect high levels of expression even if the second transfection was performed long after the first one, at a time when most of the transiently introduced episomal DNA has been eliminated. To address this possibility, the cells from Table 3, selected for antibiotic resistance for three weeks, were transfected again once or twice and selected for the incorporation of additional DNA resistance markers. The tertiary, or the tertiary and quaternary transfection cycles, were performed with combinations of pMAR or pMAR-SV40EGFP, and analyzed for GFP expression as before.

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Table 9

Tertiary transfection		Quaternary transfection			
Type of plasmid	EGFP- fluorescence	Fold increase	Type of plasmid	EGFP- fluorescence	Fold increas e
pMAR	18368	2.2	pMAR pMAR- SV40EGFP	43'186 140'000	2.4 7.6
pMAR-SV40EGF	16544	2.0	pMAR- SV40EGFP pMAR	91'000 33'814	5.5 2.0

30 Table 9. MARs act as facilitator of DNA integration.

The pMAR-SV40EGFP/ pMAR-SV40EGFP secondary transfectants were used in a third cycle of transfection at the end of the selection process. The tertiary transfection was accomplished with pMAR or pMAR-SV40EGFP, and pTKhygro as selection plasmid, to give tertiary transfectants. After 24 hours, cells were transfected again with either plasmid and pSVdhfr, resulting in the quaternary transfectants which were selected in growth medium containing 500 μg/ml G-418 and 5μg/ml puromycin, 300 μg/ml hygromycin B and 5μM methotrexate. The secondary transfectants initially exhibited a GFP fluorescence of 8300. The fold increases correspond to the ratio of fluorescence obtained from two consecutive transfections as compared to the sum of

fluorescence obtained from the corresponding independent transfections. The fold increases that were judged significantly higher are shown in bold, and correspond to fluorescence values that are 2-fold higher than the addition of those obtained from the independent transfections.

These results show that loading more copies of pMAR or pMAR-SV40EGFP resulted in similar 2-fold enhancements of total cell fluorescence. Loading even more of the MAR in the quaternary transfection further enhanced this activity by another 2.4-fold. This is consistent with our hypothesis that newly introduced MAR sequences may integrate at the chromosomal transgene locus by homologous recombination and thereby further increase transgene expression.

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When the cells were transfected a third and fourth time with the pMAR-SV40EGFP plasmid, GFP activity further increased, once again to levels not expected from the addition of the fluorescence levels obtained from independent transfections. GFP expression reached levels that resulted in cells visibly glowing green in day light (Fig. 14). These results further indicate that the efficiency of the quaternary transfection was much higher than that expected from the efficacy of the third DNA transfer. indicating that proper timing between transfections is crucial to obtain the optimal gene expression increase, one day being preferred over a three weeks period. We believe that MAR elements favour secondary integration events in increasing recombination frequency at their site of chromosomal integration by relaxing closed chromatin structure, as they mediate a local increase of histone acetylation (Yasui, D., et al., SATB1 targets chromatin remodelling to regulate genes over long distances. Nature, 2002, 419(6907); p. 641-5.1. Alternatively, or concomitantly, MARs potentially relocate nearby genes to subnuclear locations thought to be enriched in trans-acting factors, including proteins that can participate in recombination events such as topoisomerases. This can result in a locus in which the MAR sequences can bracket the pSV40EGFP repeats, efficiently shielding the transgenes from chromatin-mediated silencing effects.

Example 16: Use of MARs identified with SMAR Scan® II to increase the expression of a recombinant protein.

35 Four MAR elements were randomly selected from the sequences obtained from the analysis of the complete human genome sequence with SMAR Scan® or the combined method. These are termed 1 6, 1 42, 1 68, (where the first number represents the chromosome from which the sequence originates, and the second number is specific to the predicted MAR along this chromosome) and X S29, a "super" 40 MAR identified on chromosome X. These predicted MARs were inserted into the pGEGFPControl vector upstream of the SV40 promoter and enhancer driving the expression of the green fluorescent protein and these plasmids were transfected into cultured CHO cells, as described previously (Zahn-Zabal, M., et al., Development of stable cell lines for production or regulated expression using matrix attachment regions. 45 J Biotechnol, 2001, 87(1); p. 29-42). Expression of the transgene was then analyzed in the total population of stably transfected cells using a fluorescent cell sorter (FACS) machine. As can be seen from Fig. 19, all of these newly identified MARs increased the expression of the transgene significantly above the expression driven by the chicken lysosyme MAR, the "super" MAR X S29 being the most potent of all of the newly 50 identified MARs.

Example 17: Effect on hematocrit of in vivo expression of mEpo by electrotransfer of Network system with and without Human MAR (1-68).

5 The therapeutic gene encodes EPO (erythropoietin), an hormone used for the treatment of anemia. The EPO gene is placed under the control of a doxycycline inducible promoter, in a gene switch system described previously called below the Network system (Imhof, M. O., Chatellard, P., and Mermod, N. (2000). A regulatory network for efficient control of transgene expression. J. Gene. Med. 2, 107-116). The EPO and regulatory genes are then injected in the muscle of mice using an *in vivo* electroporation procedure termed the electrotransfer, so that the genes are transferred to the nuclei of the muscle fibers. When the doxycycline antibiotic is added to the drinking water of the mice, this compound is expected to induce the expression of EPO, which will lead to the elevation of the hematocrit level, due to the increase in red blood expression of EPO, higher levels of hematocrit would be expected.

In vivo experiments were carried out on 5 week-old C57BL6 female mice (Iffa Credo-Charles River, France). 30µg of plasmid DNA in normal saline solution was delivered by trans-cutaneous injections in the tibialis anterior muscle. All injections were carried out under Ketaminol (75 mg/kg) and Narcoxyl (10 mg/kg) anesthesia. Following the intramuscular injection of DNA, an electrical field was applied to the muscle. A voltage of 200 V/cm was applied in 8 ms pulses at 1Hz (Bettan M, Dartell R, Caillaud JM, Soubrier F, Delaere P, Branelec D, Mahfoudi A, Duverger N, Scherman D. 2000. "High-level protein secretion into blood circulation after electric pulse-mediated gene transfer into skeletal muscle". Mol Ther. 2: 204-10).

16 mice were injected by the Network system expressing EPO without the 1_68 MAR and 16 other mice were injected with the Network system incorporating the MAR in 5' of the promoter/enhancer sequences driving the expression of the activator and EPO genes. In each group, half of the mice were submitted to doxycycline in drinking water from the beginning of the experiment (day 0 – the day of electrotransfer) and in the other half, doxycycline was put in drinking water starting at day 21.

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35 Blood samples were collected using heparinated capillaries by retro-orbital punction at different times after the injection of plasmids. Capillaries were centrifugated 10 minutes at 5000 rpm at room temperature and the volumetric fraction of blood cells is assessed in comparison to the total blood volume and expressed as a percentile, determining the hematocrit level.

As can be deduced from Fig. 16 The group of mice injected by MAR-network, induced from the beginning of the experiment, display a better induction of the hematocrit in comparison of mice injected by original network without MAR. After 2 months, haematocrits in "MAR-containing group" is still at values higher (65%) than normal hematocrit levels (45-55%).

More importantly, late induction (day 21) is possible only in presence of MAR but not from mice where the Network wwas injected without the MAR. Thus the MAR likely protects the transgenes from silencing and allows induction of its expression even after prolong period in non-inducing conditions.

Overall, the MAR element is able to increase the expression of the therapeutic gene as detected from its increased physiological effect on the hematocrit.

CLAIMS

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A purified and isolated DNA sequence having protein production increasing activity characterized in that said DNA sequence comprises

- a) at least one bent DNA element,
 - b) and at least one binding site for a DNA binding protein.
- The purified and isolated DNA sequence of claim 1 characterized in that the bent DNA element contains at least 10% of dinucleotide TA, and/or at least 12% of dinucleotide AT on a stretch of 100 contiquous base pairs.
- The purified and isolated DNA sequence of claim 2 characterized in that the bent DNA element contains at least 33% of dinucleotide TA, and/or at least 33% of dinucleotide AT on a stretch of 100 contiguous base pairs.
- 4. The purified and isolated DNA sequence of claims 1 to 2, characterized in that it comprises a MAR nucleotide sequence selected from the group comprising the sequences SEQ ID Nos 1 to 27, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- 5. The purified and isolated DNA sequence of claims 1 to 2, characterized in that it comprises a cLysMAR element and/or fragment, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- The purified and isolated DNA sequence of claim 5, characterized in that said part thereof is a nucleotide sequence selected from the B, K and F regions.
- 30 7. The purified and isolated sequence of claims 1 to 6, characterized in that said DNA binding protein is a transcription factor.
 - 8. The purified and isolated sequence of claim 7, characterized in that the transcription factor is selected from the group comprising the polyQpolyP domain proteins.
 - 9. The purified and isolated sequence of claim 7, characterized in that the transcription factor is selected from the group comprising SATB1, NMP4, MEF2, S8, DLX1, FREAC7, BRN2, GATA 1/3, TATA, Bright, MSX, AP1, C/EBP, CREBP1, FOX, FreaC7, HFH1, HNF3alpha, Nix25, POU3F2, Pit1, TTF1, XFD1, AR, C/EBPgamma, Cdc5, FOXD3, HFH3, HNF3 beta, MRF2, Oct1, POU6F1, SRF, V\$MTATA_B, XFD2, Bach2, CDP CR3, Cdx2, FOXJ2, HFL, HP1, Myc, PBX, Pax3, TEF, VBP, XFD3, Brn2, COMP1, Evil, FOXP3, GATA4, HFN1, Lhx3, NKX3A, POU1F1, Pax6, TFIIA and Vmw65 or a combination of two or more of these transcription factors.
 - 10. A purified and isolated cLysMAR element and/or fragment having protein production increasing activity, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
 - 11. The cLysMAR element and/or fragment of claim 10 consisting of at least one nucleotide sequence selected from the B, K and F regions.

12. A synthetic MAR sequence comprising natural MAR elements and/or fragments assembled between linker sequences.

- 13. The synthetic MAR sequence of claim 12, characterized in that the MAR comprises a cLysMAR element and/or fragment, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- The synthetic MAR sequence of claims 12 to 13, characterized in that the linker
 sequences are BgIII-BamHI linker.

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- 15. A method for identifying a MAR sequence using a Bioinformatic tool comprising the computing of values of one or more DNA sequence features corresponding to DNA bending, major groove depth and minor groove width potentials and melting temperature.
- The method for identifying a MAR sequence using a Bioinformatic tool according to claim 15, characterized in that said Bioinformatic tool contains algorithms, adapted to the use of profiles or weight-matrices, to compute values for one or more of said DNA
 sequence features corresponding to DNA bending, major groove depth and minor groove width potentials, and melting temperature.
 - 17. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 16, characterized in that said profiles or weight-matrices are based on dinucleotide recognition.
 - 18. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 17, characterized in that said Bioinformatic tool computes values for all of said DNA sequence features,
 - 19. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 18, characterized in that said Bioinformatic tool is SMAR Scan®®.
- 20. The method for identifying a MAR sequence using a Bioinformatic tool according to claims 15-19, characterized in that the identification of one or more DNA sequence features further comprises a feature corresponding to one or more binding sites for DNA binding proteins.
- 21. The method for identifying a MAR sequence using a Bioinformatic tool according 40 ° to claim 20, characterized in that said DNA binding protein is a transcription factor.
 - 22. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 21, characterized in that the transcription factor is selected from the group comprising polyQpolyP domain proteins or transcription factors.
 - 23. The method for identifying a MAR sequence using a Bioinformatic tool according to claims 20 to 21, characterized in that the DNA binding protein is selected from the group comprising SATB1, NMP4, MEF2, S8, DLX1, FREAC7, BRN2, GATA 1/3, TATA, Bright, MSX, AP1, C/EBP, CREBP1, FOX, Freac7, HFH1, HNF3alpha, Nkx25, POU3F2, Pit1, TTF1, XFD1, AR, C/EBPgamma, Cdc5, FOXD3, HFH3, HNF3 beta, MBF2, Cdf, BOUGE1, SPE, WMTATA, B. XED2, Bach2, CDR, CG3, Cdv2, FOXL9.

MRF2, Oct1, POU6F1, SRF, V\$MTATA_B, XFD2, Bach2, CDP CR3, Cdx2, FOXJ2, HFL, HP1, Myc, PBX, Pax3, TEF, VBP, XFD3, Bm2, COMP1, Evil, FOXP3, GATA4,

HFN1, Lhx3, NKX3A, POU1F1, Pax6, TFIIA and Vmw65 or a combination of two or more of these transcription factors.

- 24. The method for identifying a MAR sequence using a Bioinformatic tool according to claims 15-23, characterized in that values for the identification of DNA bending are comprised between 3 to 5 °.
- 25. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 24, characterized in that values for the identification of DNA bending are comprised between 3.8 to 4.4°.
 - 26. The method for identifying a MAR sequence using a Bioinformatic tool according to claims 15-25 characterized in that values for the identification of the major groove depth are comprised between 8.9 to 9.3 Å and values for the identification of minor groove width are comprised between 5.2 to 5.8 Å.

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- 27. The method for identifying a MAR sequence using a Bioinformatic tool according to claims 26, characterized in that values for the identification of major groove depth are comprised between 9.0 to 9.3 Å and values for the identification of minor groove width are comprised between 5.4 to 5.7 Å.
- 28. The method for identifying a MAR sequence using a Bioinformatic tool according to claims 15-27, characterized in that the melting temperature is comprised between 55 to 75 °C.
- 29. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 28, characterized in that the melting temperature is comprised between 55 to 62 ° C.
- 30 30. The method for identifying a MAR sequence using a Bioinformatic tool of claims 15 to 29, characterized in that it further comprises at least one filter predicting DNA binding sites for DNA transcription factors.
- 31. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 30, characterized in that the filter is applied before or after the Bioinformatic tool.
 - 32. The method according to claims 30 to 31, characterized in that the filter detects clusters of DNA binding sites using profiles or weightmatrices.
 - The method according to claim 32, characterized in that the filter detects densities of clusters of DNA binding sites.
- A method for identifying a MAR sequence characterized in that it comprises at
 least one filter detecting clusters of DNA binding sites using profiles or weightmatrices.
 - 35. A purified and isolated MAR DNA sequence identifiable according to claims 15 to 33 or claim 34.
- 50 36. The purified and isolated MAR DNA sequence of claim 35, containing at least 10% of dinucleotide TA on a stretch of 100 contiguous base pairs.

37. The purified and isolated MAR DNA sequence of claim 36, containing at least 33% of dinucleotide TA on a stretch of 100 contiguous base pairs.

- 38. The purified and isolated MAR DNA sequence of claims 35 to 37, further containing at least 12% of dinucleotide AT on a stretch of 100 contiguous base pairs.
 - 39. The purified and isolated MAR DNA sequence of claim 38, further containing at least 33% of dinucleotide AT on a stretch of 100 contiguous base pairs.
- 40. The purified and isolated MAR DNA sequence of any of claims 35 to 39, comprising a sequence selected from the sequences SEQ ID Nos 1 to 27, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- 15 41. The purified and isolated DNA sequence of claim 40, comprising a sequence selected from the sequences SEQ ID Nos 24 to 27, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- 20 42. The use of a purified and isolated DNA sequence comprising a first isolated matrix attachment region (MAR) nucleotide sequence which is a MAR nucleotide sequence selected from the group comprising:
 - a purified and isolated DNA sequence of claims 1 to 9, - a purified and isolated MAR DNA of claims 35 to 41,
- 25 the sequences SEQ ID Nos 1 to 27,

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- a purified and isolated cLvsMAR element and/or fragment.
- a synthetic MAR sequence of claims 12 to 14.
- a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants for increasing 30 , protein production activity in a eukaryotic host cell.
 - 43. The use of the purified and isolated DNA sequence of claim 42, characterized in that said purified and isolated DNA sequence further comprises a promoter operably linked to a gene of interest.
 - 44. The use of the purified and isolated DNA sequence of claims 42 or 43, characterized in that said purified and isolated DNA sequence further comprises at least a second isolated matrix attachment region (MAR) nucleotide sequence which is a MAR nucleotide sequence selected from the group comprising:
 - a purified and isolated DNA sequence of claims 1 to 9.
 - a purified and isolated MAR DNA of claims 35 to 41.
 - the sequences SEQ ID Nos 1 to 27,
 - a purified and isolated cLvsMAR element and/or fragment.
 - a synthetic MAR sequence of claims 12 to 14.
- 45 a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants for increasing protein production activity in a eukaryotic host cell.
- 45. The use of the purified and isolated DNA sequence of claim 44, characterized in 50 that said first and at least second MAR sequences are located at both the 5' and the 3' ends of the sequence containing the promoter and the gene of interest.

46. The use of the purified and isolated DNA sequence of claim 44, characterized in that said first and or at least second MAR sequences are located on a sequence distinct from the one containing the promoter and the gene of interest.

- 5 47. The use of the purified and isolated DNA sequence of any of claims 42 to 46, characterized in that said purified and isolated DNA sequence is in the form of a linear DNA sequence as vector.
- 48. A method for transfecting a eukaryotic host cell, said method comprising a) introducing into said eukaryotic host cell at least one purified DNA sequence comprising at least one DNA sequence of interest and/or at least one purified and isolated DNA sequence consisting of a MAR nucleotide sequence or other chromatin modifying elements.
- b) subjecting within a defined time said transfected eukaryotic host cell to at least one additional transfection step with at least one purified DNA sequence comprising at least one DNA sequence of interest and/or with at least one purified and isolated DNA sequence consisting of a MAR nucleotide sequence or other chromatin modifying elements
 - c) selecting said transfected eukaryotic host cell.
- 49. The method of claim 48, characterized in that said DNA sequence of interest is a gene of interest coding for a protein operably linked to a promoter.
- 50. The method of claims 48 and 49, characterized in that the selected transfected eukaryotic host cells are high protein producer cells with a production rate of at least 10 pg per cell per day.
 - 51. The method of claims 48-50, characterized in that the MAR nucleotide sequence is selected from the group comprising:
 - a purified and isolated DNA sequence of claims 1 to 9.
 - a purified and isolated MAR DNA of claims 35 to 41,
 - the sequences SEQ ID Nos 1 to 27.

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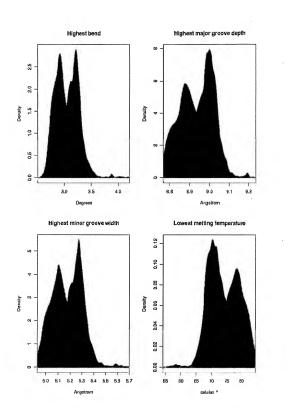
- a purified and isolated cLysMAR element and/or fragment,
- a synthetic MAR sequence of claims 12 to 14,
- 35 a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- The method of claims 48-50, characterized in that the MAR nucleotide is a purified and isolated sequence according to claims 1 to 9, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
 - 53. The method of claims 48 to 52, characterized in that the defined time corresponds to intervals related to the cell division cycle.
 - 54. The method of claim 53, characterized in that the defined time is the moment the host cell just has entered into a second cell division cycle.
- 55. A method for transfecting a eukaryotic host cell, said method comprising cotransfecting into said eukaryotic host cell at least one first purified and isolated DNA sequence comprising at least one DNA sequence of interest, and a second and isolated purified DNA comprising at least one MAR nucleotide selected from the group comprising:

- a purified and isolated DNA sequence of claims 1 to 9,
- a purified and isolated MAR DNA of claims 35 to 41,
- the sequences SEQ ID Nos 1 to 27,
- a purified and isolated cLysMAR element and/or fragment,
 - a synthetic MAR sequence of claims 12 to 14,
- a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- 56. A process for the production of a protein wherein
- 10 a) a eukaryotic host cell transfected according to claims 48 to 54 or claim 55, is cultured in a culture medium under conditions suitable for expression of said protein and
 - b) said protein is recovered.

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- 15 57. A eukaryotic host cell transfected according to any one of claims 48 to 54 or claim 55.
 - 58. A cell transfection mixture or kit comprising at least one purified and isolated DNA sequence according to claims 1 to 9, 10 to 11, 12 to 14 or 35 to 41.
 - 59. A transgenic organism characterized in that at least some of its cells have stably incorporated at least one DNA sequence of claims 1 to 9, 10 to 11, 12 to 14 or 35 to 41.
- 60. A transgenic organism characterized in that its genome has stably incorporated at least one DNA sequence of claims 1 to 9, 10 to 11, 12 to 14 or 35 to 41.
 - 61. The transgenic organism of claims 59 and 60 characterized in that some of its cells have been transfected according to the method of claims 48 to 54 or claim 55.
- 30 62. A computer readable medium characterized in that it comprises computerexecutable instructions for performing the method for identifying a MAR sequence of claims 15 to 33 and/or claim 34.

FIG.1



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FIG.2

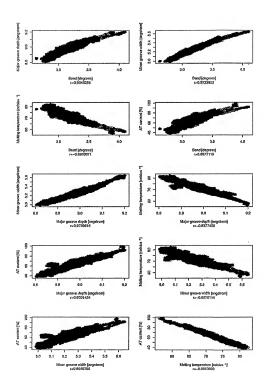


FIG.3

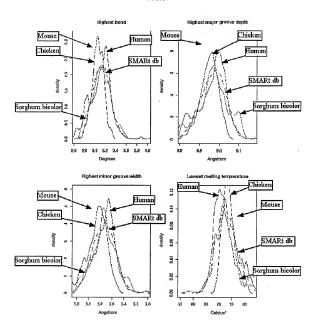
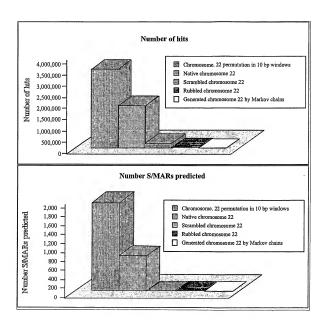


FIG.4



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FIG.5

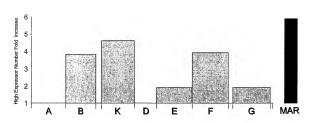


FIG.6

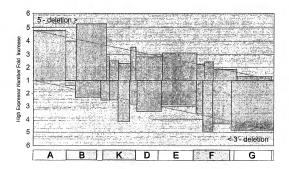


FIG.7

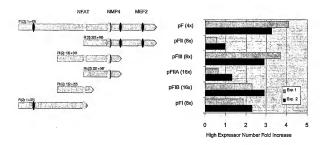


FIG.8

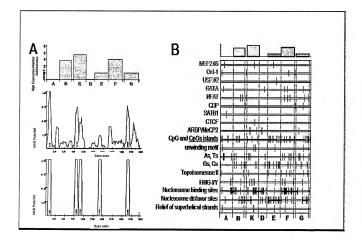
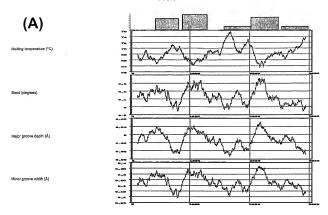
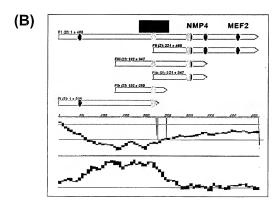


FIG.9





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FIG.10

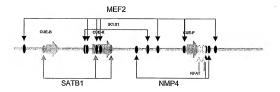
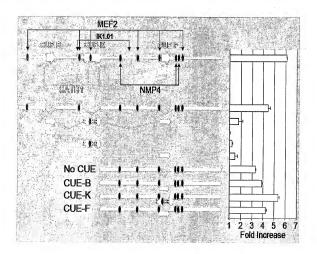
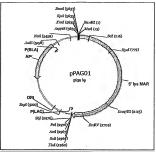
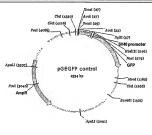


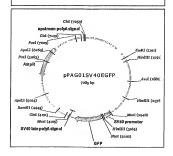
FIG.11



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FIG.13

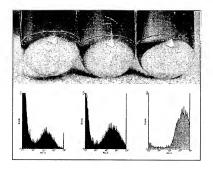
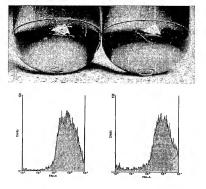
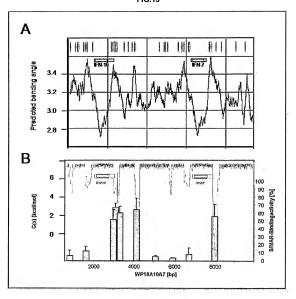


FIG.14



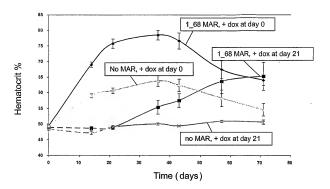
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FIG.15



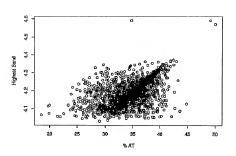
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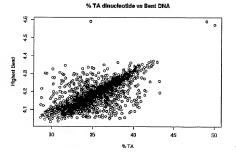
FIG.16



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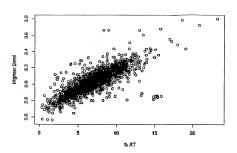
FIG.17





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FIG.18



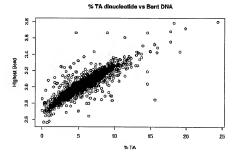


FIG.19

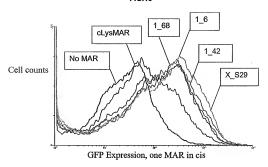
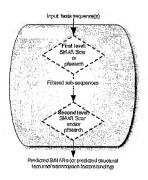


FIG.20



SEL PCT 012.ST25 SEQUENCE LISTING

<110> Selexis S.A.

<120> HIGH EFFICIENCY GENE TRANSFER AND EXPRESSION IN MAMMALIAN CELLS BY A MULTIPLE TRANSFECTION PROCEDURE OF MAR SEQUENCES

<130> SEL PCT O12

<150> US 60/513,574

<151> 2003-10-24

<150> EP 04 002 722.9

<151> 2004-02-06

<160> 241

<170> Patentln version 3.1

<210> 1

<211> 320

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

SEL PCT 012.ST25

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<223> MAR of human chromosome 1, nt from 36686 to 37008

<220>

<221> misc binding

<222> (1)..(320)

<223> MAR of human chromosome 1, genomic contig; 36686 to 37008

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taattatata ttacattata taatatataa taatattata taattatata ttacattata 180

gtatataata ttatataata

320

<210> 2

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<220>

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<222> (1)..(709)

<223> MAR of human chromosome 1, nt from 142276 to 142984

SEL PCT 012 ST25

<220>

<400> 2

<221> misc binding

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<223> MAR of human chromosome 1, genomic contig; 142276 to 142984

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tttatattat aattatgttt tgcattatat atttcatatt atatatacc

<210> 3

<211> 409

<212> DNA

<213> Homo sapiens

<220>

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SEL PCT 012 ST25

<222> (1)..(409)

<223> MAR of human chromosome 1, nt from 1368659 to 1369067

<220>

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<211> 394

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

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<223> MAR of human chromosome 1, genomic contig; 2839089 to 2839482 Seite 4

SEL PCT 012.ST25

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tatgtatata tacacacata tgtatatacg tatatatgta tatatacaca catatgtata	180
tatgtatata tacacacata tgtatatacg tatatatgta tatatacaca catgtgtata	240
tatatataca catatgtata tatgtatata tacacacata tgtatatatg tgtatgtata	300
tatacacaca tatgtatata tacacatata tatgtatata tacacacata cttatatata	360
cacatatata tgtatatata cacatatgta taca 394	

<210> 5

<211> 832

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

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<400> 5

SEL PCT 012.ST25

<210> 6

<211> 350

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<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(350)

<223> MAR of human chromosome 1, genomic contig; 831495 to 831844

SEL PCT 012.ST25

<210> 7

<211> 386

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(386)

<223> MAR of human chromosome 1, genomic contig; 1447225 to 1447610

<400> 7

acatttaatt taattatata ctgctatata taattaaatc tatatatcta tataacttat 60
aatttatttt aatttaatta tataactat atagttatat atacatatat gtaattatat 120
atagtataat tatagtatat atgtatatat aatgtaagta aatatatagt atatatttat 180
atatactata tatttataca tatgtcttta tatatactaa tatatataca catatgtaat 240
atgtacatat ggcatatatt ttatagtgta tatatacata tatgtaatat atatagtaat 300
atgtaaatat atagtacata tttaattata tggtaatata tacacatata tgtaatatgt 360
gtattatagt acatatttta tagtat 386

<210> 8

<211> 585

<212> DNA

<213> Homo sapiens

<220>

SEL PCT 012.ST25

<221> misc binding

<222> (1)..(585)

<223> MAR of human chromosome 1, genomic contig; 4955365 to 4955949

<400> 8
 atacacacat atacacatat gracgtatat atacatata tacacacata tacacatatg
 60
 tacgtatata tacatatata acacacatat acacatatgt acgtatatat actatatata
 120
 cacacacatata cacatatgta cgtatatata ctatatatac acacatatgtac
 gtatatatac tatatataca cacatataca catatgtacg tatatattat atacacaca
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 atacacatatgt tacgtatata tacacacatat acacacata
 atacacatatgt tacgtatata tacacacatat acacacatat
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 acacatatgtac gtatatatac cacatatgtac gtatatatac cacacatatac
 acatatgtac gtatatatac tatatataca cacatataca catatgtacg tatatatac
 atatatacaca gtatatatac tatatataca cacatataca catatgtacg tatatatac
 atatatacca atacacatac gtatatacgt acatatatatacgta

<210> 9

<211> 772

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(772)

<223> MAR of human chromosome 1, genomic contig; 5971862 to 5972633

SEL PCT 012.ST25

<400> 9 agtaaacata tatatagtaa atatatatag totatatata gtaaatatat atagtocata 60 tatatagtoc atatatatag totatatata otaaatatat agtotatata tatagtaaat 120 atatatagtg tatatatagt aaatatatat agtaaatata tatatactat atatagtaaa 180 240 300 360 tatatagtat atatatagta aatatatata tagtatatat atagtaaata tatatagtat 420 atatatagta aatatatata gtatatatat agtaaatata tatagtatat atatagtaaa 480 tatatataca cigitatatat atagtaaata tatatacaci giatatatat agtaaatata 540 tatacactgt atatatatag taaatatata tacactgtat atatatagta aatatatata 600 cactotatat acatagtaaa tatatataca ctotatatac atagtaaata tatatacact 660 gtatatacat agtaaatata tatacactgt atatacatag taaatatata tacagtgtat 720 atacatagta aatatatata cagtgtatat acatagtaaa tatatataca gt 772

<210> 10

<211> 304

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(304)

<223> MAR of human chromosome 1, genomic contig; 6221897 to 6222200

<400> 10

SEL PCT 012.ST25

atta

304

<210> 11

<211> 311

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(311)

<223> MAR of human chromosome 1, genomic contig; 9418531 to 9418841

<400> 11

tatatataat atttatatat aatattcatg tatttatata taaatattta tatatttata

tataaatatt tatatattta tatataaata tttatatatt tatatataat atttatacat 120

tataatttat a 311

<210> 12

<211> 302

60

SEL PCT 012.ST25

<212> DNA <213> Homo sapiens <220> <221> misc binding <222> (1)..(302) <223> MAR of human chromosome 1, genomic contig: 15088789 to 15089090 <400> 12 atataatata tatattatat atataaatat atataaatat ataacatata tattatatat 60 tatatattat atataaaat atataaaat atataacata tatattatat atataaatat 180 atattatata tttatatata taatatatat aaatatataa tatatatta tatatataa 240 at 302 <210> 13 <211> 461 <212> DNA <213> Homo sapiens <220> <221> misc binding

<223> MAR of human chromosome 1, genomic contig; 6791827 to 6792287

<222> (1)..(461)

SEL PCT 012.ST25

<400> 13	
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atatattata tatacacata tataatatat attatatata	120
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catatataat atatattata tatacacata tataatatat attatatata	240
atatatatta tatatacaca tatgtaatat atattataca cacacatata atatatatta	300
tatacacata tataatatat attatatata catatataat atatattata tatacacata	360
tataatatat attatatata cacatatata atatatat	420
aatatataca catatataat atatatatta tatatgcaca t 461	
<210> 14	
<211> 572	
<212> DNA	
<213> Homo sapiens	
<220>	
<221> misc_binding	
<222> (1)(572)	
<223> MAR of human chromosome 1, genomic contig; 163530	to 164101
<400> 14 atattataat tatatatatt atatataatt atataaaata tatattat	0

SEL PCT 012.ST25

<210> 15

<211> 357

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(357)

<223> MAR of human chromosome 1, genomic contig; 1842332 to 1842688

<400> 15

<210> 16

<211> 399

<212> DNA

SEL PCT 012.ST25

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(399)

<223> MAR of human chromosome 1, genomic contig: 2309560 to 2309958

<400> 16

attatatata atatatata tatattatat atatcaagca gcagatataa tatataatat

gtatattata taatataa tatatataat atatattgta tattatataa tatataatat 180

atataatata tattgtatat tatataatat ataatatatg taatatata tgtaatatat 240

tatattacat atattacgta atatatgtta tatattacat ataatatata acatatatta 360

cgtaatatat gtaatatatt acatataata tatacatta 399

<210> 17

<211> 394

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(394)

<223> MAR of human chromosome 1, genomic contig; 2231759 to 2232152

SEL PCT 012.ST25

<400> 17
atatatactt ataaattata tacttatata tacttataaa ttatatactt ataaattata
ataaattata tacttatata tacttataaa ttatatactt ataaattata
tacttatata tacttataaa ttatatactt ataaattata tacttatata
tacttataaa ttatatactt atatatactt ataaattata tacttatata
tacttataaa ttatatactt atatataatt ataaattata tacttatata taattataaa
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ataatataatt ataaattata tacatatata taattataaa ttatatacat atataatta
aaattataat catatataat taaaattat ataa
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aaaattataa catatataa taaaattat ataa
aaaattataa catatataa taaaattata aaa

<210> 18

<211> 387

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(387)

<223> MAR of human chromosome 1, genomic contig: 7406524 to 7406910

SEL PCT 012.ST25 387

acataatata ttatatataa tatatta

<210> 19

<211> 370

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(370)

<223> MAR of human chromosome 1, genomic contig; 9399572 to 9399941

<400> 19

<210> 20

<211> 377

<212> DNA

<213> Homo sapiens

377

SEL PCT 012 ST25

<221> misc_binding

<222> (1)..(377)

<223> MAR of human chromosome 1, genomic contig; 12417411 to 12417787

<400> 20

atatatataa tttatat

<210> 21 <211> 1524

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1524)

<223> MAR of human chromosome 1, genomic contig; 1643307 to 1644830

<400> 21

tataaatata tataaatata taaatatata taaatatata aatatataa aatatatata 60
aatatataaa aatatataaa tatatataaa tatatataaa tatataaaa cataaaaaata 120

SEL PCT 012.ST25

tatataaata tataaaata tataaaata tataaatata taaatatata aaaatataca 180	
aatatataaa tatatacata aatatatata aatatatat	
aatatataaa tatatataaa tatatataaa tatataaaa tatataaaaa tatatataaa 300	
tatataaata tataaaaata tatataaata tataaaatata taaaatatata taaatatata 360	
aatatataaa taaatataag tatttatgaa tatatatgaa tatataaata tataaaaaat 420	
atatataaat atataaatat atataaatat ataaatatat acatatatac atatataaat 480	
aaataaatat aagtatttat gaatatatat gaatatataa atatataaa aatatatat	
aatatataaa tatatataaa tataaatata taaaaatata taaaaatata tataaatata 600	
taaatatata taaatatata aatatatata aatatatata aatatataaa tatatataaa 660	
tatatataaa tatataaata tataaatata tataaatata tataaatata taaaatataa 720	
aatataaata tataaatata tataaatata tataaatata taaatatata aaatatata 780	
taaatatata taaatatata taaatatata aatatatata aatatatata taaatatata 840	
taaatatata aatatataaa tatataaaaa tatataacaa tatataaata tatataaaaa 900	
tatataacaa tatataaata taaatatata taaaaatata taacaatata taaatataaa 960	
tatatataaa tatataaata taaatataaa aaatatatat aaatatataa atatatataa 1020	
atatataaat gtataaatat atataaaaat atataacaat atataaatat ataaatatat 1080	
aacaatatat aaatatataa aaatatataa caatatataa atataaaatat atataaaaat 114	3
atataacaat atataaatat aaatatata ataaatatat aaatataaat ataaaaaa)
tatataaata tataaatata tatataaata tataaaata tataaaatgta taaatatata 1260	
taaatatata aatatataaa aatatataaa tatatataaa tatatataaa tatataaata 1320	
taaatatata aatatataa aatatataaa tataaatata taaacatata taaatatata 1380	
taaataaaca tatataaaga tatataaaga tataaagata tataaatata taaatatata 144)
aagatatata aatatataaa gatatataaa tatataaaga tatataaata tataaagata 150	3
tataaatata atatataaat atat 1524	

SEL PCT 012.ST25

<211> 664

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(664)

<223> MAR of human chromosome 1, genomic contig; 1398763 to 1399426

<400> 22

<210> 23

<211> 1428

<212> DNA

SEL PCT 012.ST25

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(1428)

<223> MAR of human chromosome 2, genomic contig; 17840365 to 17841792

<400> 23 60 atattatata tratatatat tatatattat atatttatat ataatatata totaatatat 120 atattagata taatatatat ctaatatata tatattttat atatataata tatctctaat 180 atatatattt tatatotata taatatatct ctaatatata tatattttat atotatataa tatatctcta atatatatat tttttatata taatatatct ctaatatata tattttatat 300 atataatata tatotaatat atataatata tatattagat atatataaaa tatatatgat 480 tacaatatat attatatatt ttatatacaa tatatattat atatattta tatttttata 540 600 660 ataaattata atattitta tatatataat atotattita tatataatat attataatat atattttata tataatatat tataatatat attttatata taatatatta taatatatat 780

SEL PCT 012.ST25

<210> 24

<211> 4624

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(4624)

<223> MAR 1_6 of chromosome 1

<400> 24

ggatcttaaa tctattitat ttattattt ttcatgtggc caataccctc caccccttc 60

ttctgtctct ttcaacttat tgtggttacc ttgaggctac ctgagacagt aggcttgggt 120
ggggaagtat gcattctaag tgtaaagttt gatgagcttt gacaaatgtc aacccatgta 180
ccagaacatt ttcatcaccc ataaaatctc ccttgtgtca cttgccagtc agtgtctatt 240
ctagtatcca actcctggct ccaagaaacc attgaactgt tttctgtcac tataaattag 300
atttgtcttt tctagagttt catgtaaatg gaatcataca ctaagtactc tttgtgcctg 360
gcttctgctc agcataatgt ttttgagaat cattcatgct gctgcatgtt ttcagtagtt

SEL PCT 012 ST25

catttttta aataggtgaa ttgtaactca ttctgtgaat ataccatatt ctgtcttcca 480 tttatctott agtggatctt taggtcgttt ctagttttgg gctattgcaa ataaagctgc 540 tgtaaatatt aatgcacaag ttttccatgt tcatatgttt catttcactt aggaaaatac 600 ctaagagagg aattgcacat attaaaaaaa ttttaaaaaac tactaagctg ttctccaaaa 660 tggttgtaca atttttattc ccaagagcaa tatgagtgtt taattgctcc acattctcac 720 caacactigg tgcttgttag ttttattttc attgttttca ttgttatgtc tgtgaggcag 780 cattgatgtg catgtctctg agtgtcatct tagcggtgat gctgagcatc agttcacgtc 840 cttataggcc gtttgtatat ctgctttgtg aaatgtctgt tcaaatcttt tgcctatttt 900 aaattgagtt gtgttcgtct tcttaggatt aagtaatgag ttaaaaatat ttctgataca 960 aatotttoat tatatattic taatgottic toatotatag titattitot catattotti 1020 aactgtatct tttgaagagc aaattttact tttgattatg cccaatttat caagttttta 1080 tatggctctt ttgattatgc ccataatcac attagacttt gcctaaccca agtttgcaga 1140 gattittict titatgetti tatetagaaa tittgtagit ttaggttita aaaaagttia 1200 atttatttat ttgagacagg gtattgetet ttacatatac tggagtgeag tgatgeaate 1260 atggctcact gcagcctcaa cctcttgggc tcaagcggtt ctcccatctc agagtcctga 1320 gtagctggcc aggtgcatgc cagcttcaat gtgtttttca tttgcatttc cctgataatt 1380 attgacgttg agcatttttt tcatatatca gttagctatt tgtacgtctt cttttgagaa 1440 acatctattc gggtcttttg cccattttaa agtcagatgg tttgtttgtc agctattgag 1500 ttgtttgagt tccttgtata ttctggatat taccatcttg tcagatgcac agtttgcaaa 1560 tittittitti ctattitgia ggttgtctct ttctctgttg tttcctccgg tatgcagaag 1620 ttttttagtg tgatgtaatt tcatttgtct gtttttgctt ttgttgcctg tactttctta 1680 ttettateea aaaaatetti atetagatea atgicaegaa gagittetee tetgittiet 1740 tcgagtagtt ttttataatt ttgggtatac atttaagtct ttaatctatt tggaattgat 1800 ttttgcatat ggtgagagat cagagtctaa tttcatactt ttggatgtgg aaagctagtt 1860 ttttcagcac catttattga agagactgtc tcttctccaa tgtgtgttct ttgtgccttc 1920

SEL PCT 012.ST25

atcaaaaatc aattaactat acatagattt atttctatat tetetatttt attecattaa 1980 totagtttta gccttaaatt taggtctgca atttttttt ttttgtatat ggtgtgaagt 2040 aagagtcaaa gttcattatt tttcatatgg atatgtaatt actccagtac catcatttag 2100 tttgaatgga ctgtcctttc tccatggaat tacatgggca tcttttgtct gaaaccaatt 2160 atotatottt acotatotot atotttatoc atatottata gotttaatat atattaatat 2220 atataatata taatatataa atattaatat gtattatata atatatta atatattata 2280 acctataaca tatocatata cttatttata tataacatoc atotacttat ttatatatac 2460 aatatatatt tatatattat ataatatatt atatotattt atatattata tatcatatat 2520 tatatotatt tatatattat atatcatata atatatatat ttatattata tatattatat 2580 gatatataat attatataat gtattaatat atattaaacc tatatttata attctggact 2640 cactattttq tttcattqqt qtctqtqtq atctaaccct atgccaataa tgtactatct 2700 taattaccat agctttatag taagctttga aatcagatag tgtatttttt atcattgttt 2760 tttaaaataa tagtttatct ttttatttga atttgtaatc agctagtcag tttctgcaaa 2820 aagettactg ggattttget tggaattatg ttacatetgt agcatgtact atccaatatt 2880 ttaaaattaa aacttaataa ttggttcctc attcacacta ccatatgtca agtgttcaat 3000 agccacatat ggtcaatgtc ttggaaaagt caatacagta catttccatt attgcagtaa 3060 gttetgteaa acagcactat egtagaeega ttaggagaga actgaettaa cagtattgga 3120 tgetceagte aatgaacate ttttttttt teatttattt cagtagtete tgeagtatat 3180 tatagatttc agtttacata ttttgcatat attttattaa atgtataacg gtagaagtac 3240 tattattgga tgatgtgttc tatagatgta ttttaggtca agtttgttga tagtgttgtt 3300 taaatetegt atacetettg attittittat ttacttgtte tttgaattac tgagacagga 3360 atottatatc cttaactata tttotoaatt tattcacttc ttccttcagt tctgttaact 3420

SEL PCT 012.ST25

tttgcttagg tgctttttaa aaatgaaact ttcaatctct gccttttaat tgtagcattt 3480 agaccattta cattcaatgt aattatcaat atcagtttat ttaagtctga agttgtgcaa 3540 tttttcctct acctatatta taaatctttc tatatacaaa acacatacta tattttctac 3600 atatgtttta aatgacaccc ggaaagcatt gacactattt ttgctttagg ttatctttca 3660 aagatgttaa aaatgagaaa gaaatattot goatttatoo atacacttat tatttgcaaa 3720 ggttttttta aatacettig tgtagattic agttaccaac tigtattice ttcagettga 3780 agaacttaca atttcttgta ggacaggtct ctgacaacaa attatctcag cttttctttg 3840 totaaaaaag ttattgoott tattittaaa atatattito actggatatt gaattitagg 3900 tgataatctt tttttttttg ttagcacttt aaatatgtct tctaatgtcc tcttgctttc 3960 atagtttctg atgagaagtc tactgttatt agtatctctt tgtgtgtgtc tctctttttt 4020 ccctctctgc tattatggct attittttt tttttttttt tttttgtcac tggtgtcagc 4080 tgtgtgtgtg tagctgatgt tctttgagct ttagaatctg tgagtttgta gttttcatca 4200 attatttttt cittlcattc citttattta cicatgitcg tgttttattt tatattttta 4260 agaattttgt gcgtatttgt aataactgtt taaatgtcat ttgtgaattc cattgcttct 4320 aggtaggatt ctattgacag atatttttc cctgacgaga ggtcatactt tccttattct 4380 tcatgtatct agtggttttt ggttgaatac tggatatttt gaattttatg ggagtgctga 4440 attotacaat attoottaaa aatgtgttgg attttgtttt agcagatagc tatottactt 4500 gaagatcaat ttcatatttt ttgatgttca ttttttcatt tattaaagaa taggtccatg 4560 gtagagttta ctgatatcaa cetttetggt gtetetaata aatgeaacat atteaataag 4620 atcc 4624

<210> 25

<211> 3616

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<220>

<221> misc binding

<222> (1)..(3616)

<223> MAR 1_68 of chromosome 1

<400> 25 60 gactotagat tataccaacc toataaaata agagcatata taaaagcaaa tgctcttato ttgcagatcc ctgaactgag gaggcaagat cagtttggca gttgaagcag ctggaatctg 120 caattcagag aatctaagaa aagacaaccc tgaagagaga gacccagaaa cctagcagga 180 gtttetecaa acatteaagg etgagggata aatgttacat geacagggtg ageeteeaga 240 ggettgteea ttageaactg ctacagttte attateteag ggateacaga ttgtgetaec 300 tattocctac catctgaaaa cagttocttc ctatatttca tccagtttaa tatttattta 360 aaccaagaag gttaatctgg caccagctat tccgttgtga gtggatgtga aagtaccaat 420 tccattctgt tttactatta actatccttt gccttaatat gtatcagtag gtggcttgtt 480 gctaggaaat attaaatgaa tggcatgttt cataggttgt gtttaaagtt gttttttgag ttaaatcttt ctttaataat actttctgat gtcaaaaaca cttagaagtc atggtgttga 600 acatctatat agggttggat ctaaaatagc ttcttaacct ttcctaacca ctgtttttgt 660 ttgtttgttt ttaactaagc atccagtttg ggaaattctg aattagggga atcataaaag 720 gtttcatttt agctgggcca cataaggaaa gtaagatatc aaattgtaaa aatcgttaag 780 aacttctate ceatetgaag tgtgggttag gtgcctctte tetgtgetee ettaacatee 840 tattttatct gtatatatat atattcttcc aaatatccat gcatgggaaa aaaaatctga 900 tcataaaaat attttaggct gggagtggtg gctcacgcct gtaatcccag cactttggga 960 ggetgaggtg ggeggateat gaggteaaga gategagace ateetgacea atatggtgaa 1020

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SEL PCT 012.ST25

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<210> 26

<211> 4660

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

SEL PCT 012 ST25

<222> (1)..(4660)

<223> MAR 1 42 of chromosome 1

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atatacataa atatatataa atatataaa atatataaaa atatatataa atatataaat 1260

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वावावावववा वावावावववा वावावावववा वावावववववा वावाववववा वावावववावा । १३५०
ataaaaatat atataaatat ataaatatat aaatatata aaatatataa atatataaat 1380
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<210> 27

<211> 3354

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(3354)

<223> MAR X S29 of chromosome X

<400> 27
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SEL PCT 012 ST25

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SEL PCT 012.ST25

<211> 677

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(677)

<223> MAR of chromosome 1 genomic contig; 12803267..12803943

<400> 28

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<210> 29

<211> 332

<212> DNA

SEL PCT 012.ST25

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(332)

<223> MAR of chromosome 1 genomic contig; 13079684..13080015

<400> 29

taatatatat taattatatt atatatatta tataattata tattaatata tattaattat 180

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332

<210> 30

<211> 479

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(479)

<223> MAr of chromosome 1 genomic contig; 15682296..15682774

<400> 30

SEL PCT 012 ST25

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<210> 31

<211> 531

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(531)

<223> MAr of chromosome 1 genomic contig; 15694611..15695141

SEL PCT 012.ST25

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<210> 32

<211> 378

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(378)

<223> MAR of chromosome 1 genomic contig; 886276..886653

<400> 32

<210> 33

<211> 595

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<221> misc binding

<222> (1)..(595)

<223> MAR of chromosome 1 genomic contig; 3326732..3327326

<400> 33

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<210> 34

<211> 738

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(738)

SEL PCT 012.ST25

<223> MAR of chromosome 1 genomic contig; 4485716..4486453

<400> 34 ataatagata atatatatta tatgatagat atataatata ttatataata tataatatat 60
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aatatatata atatataata tatatcatat tatattgtat ataatatata tcatattata 180
ttgtatataa tatatatcat attatattgt atataatata
aatatatatc atattatatt gtatataata tatatcatat tatattgtat ataatatata 300
tcatattata ttgtatataa tatatatcat attatattgt atataatata
tattgtatat aatatatat atattatatt gtatataata tatatcatat tatattgtat 420
ataatatata tcatattata ttgtatataa tatatatcat attatattgt atataatata
tatcatatta tattgtatat aatatatatc atatattatc tattatattg tatataatat 540
atattatata ttatctatta tattgtatat aatatatatt atatattatc tattatattg 600
tatataatat atattatata ttatctatta tattgtatat aatatataat aaatatagta 660
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<210> 35

<211> 386

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(386)

<223> MAR of chromosome 1 genomic contig; 5423067..5423452 Seite 39

SEL PCT 012.ST25

<400> 35 taaatatata aaaatatata taaaaatata aaaatattta tataaatata taaaaatatt 60
tatataaata tataaatata taaatatata tttatataaa tatataaata tataaatata 120
taaatatata tttatataaa tatataaata tatatttata taaatatata aatatatata 180
aa atatataa atatatatti atataaatat ataaatatat ataaaatata taaatatata 240
tattttatat aaatatataa atatatataa aatatataaa tatatatatt ttatataaat 300
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atatatttca tatatcacat atatga 386
<210> 36
<211> 584
<212> DNA
<213> Homo sapiens
<220>
<221> misc_binding
<222> (1)(584)
<223> MAR of chromosome 1 genomic contig; 58055595806142

SEL PCT 012.ST25

<210> 37

<211> 345

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(345)

<223> MAR of chromosome 1 genomic contig; 10802644..10802988

<400> 37

<210> 38

<211> 474

<212> DNA

SEL PCT 012.ST25

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(474)

<223> MAR of chromosome 1 genomic contig; 13496468..13496941

<210> 39

<211> 483

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(483)

<223> MAR of chromosome 1 genomic contig; 2509163..2509645 Seite 42

SEL PCT 012.ST25

<400> 39	
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ctattataat atataaacta tataatatat actattataa tatatgaact attataatat	180
ataaactata tataatatat aatatgtact attataatat ataaactatt ataatataat	240
atataaacta ttataataca taaactatta taatatatat	300
tacattatgt acatactaca ttatgtatta tgtatgtata tatacacaaa atacataata	360
tataatagta ttatataata gtatatatag ttataatata tagtataatt acaatatata	420
atatggttta tatattatat atagtataat acaatataac ataatactat tatatataaa	480
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<210> 40	
<211> 641	
<212> DNA	
<213> Homo sapiens	
<220>	
<221> misc_binding	
<222> (1)(641)	
<223> MAR of chromosome 1 genomic contig; 2776349277698	89

<400> 40 tgttatatat atataacata gatattatat atacatgtta tatatataac atagatatta 60 tatatacatg ttatatatat aacatagata ttatatata aacatagata ttatatatac 120 atgttatata taacatagat attatatata catgttatat ataacagata ttatatatac 180

SEL PCT 012.ST25

atgttatata taacatag at attatatatg tatgttatat ataacataga tattatatat 240 gtttatata tatataacat atgtttaaca tatataatat ataacatgtt tatataatat 300 ataacataat tatatgttat atatgatata aaacatatat attatatacg ttatatgtaa 360 tatataacat atattgtata cgttatatgt aatatataac atatattgta tacgttatat 420 gtaatatata acatatatt gtatacgttat atgtaatata taacatatat tgcatacgtt 480 atatgtaata tataacatat attgtatac gttatatgtaa tatgtaacat atattgtata 540 cgttatatgt aatatgtaat atataacata tatatgtata 600 taacatatat ataacatata taacatatat gtatatat ataacatatat ataacatata taacatatat ataacatata ataacatata ataacatata ataacatata taacatatat gtatatata 641

<210> 41

<211> 745

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(745)

<223> MAR of chromosome 1 genomic contig; 2858703..2859447

taaatatata ttatattat aatatatatt tttotatatt atatattata tattataaat 360

SEL PCT 012.ST25

<210> 42

<211> 307

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(307)

<223> MAR of chromosome 1 genomic contig; 945522...945828

<400> 42

<210> 43

SEL PCT 012.ST25

<211> 357

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(357)

<223> MAR of chromosome 1 genomic contig; 3402743..3403099

<400> 43

<210> 44

<211> 323

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(323)

<223> MAR of chromosome 1 genomic contig; 3485830..3486152 Seite 46

SEL PCT 012 ST25

<400> 44 atattatag actatatatt tatatattta gtgtatttgt atactatata tttatatagt	60
tagtatattt gtatactata tatttatata tttagtatat ttgtatacta tatatttata	120
tatttagaat atttgtatac tatatattta tatatttagt atatttgtat actatatatt	180
tagtatattt gtatactata tatttatata tttagtatat ttgtatacta tatatttata	240
tatttagtat atttatatac tatatactta tatatttagt atatttatat actatatact	300
tatatattta gtatatttat ata 323	

<210> 45

<211> 498

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(498)

<223> MAR of chromosome 1 genomic contig; 3548336..3548833

SEL PCT 012.ST25

aatattaata taatataata toaatataat agtatataat attaatatat taatataata 420 gtatataata ttaatgtaat ataatattaa cataatgtat ataataatat aatagtatat 480

aatactaata taatataa

498

<210> 46

<211> 400

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(400)

<223> MAr of chromosome 1 genomic contig; 4595109..4595508

<400> 46

aaatatatta tattatatat tatatattat tcaatatact ataatatat ttatatatgt 60

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atattatata ttactccata taatataata tattatacat aatatattac tcagtataat 180

acataatata tataatatat tactoggtat aatatataat attatatgtt atgcaatata 240

ttattcaata taatataa tacactattc aatataatat acaatattat atataataca 360

ttattcaata taatatata tatataatat atatatttat 400

<210> 47

<211> 403

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<220>

<221> misc binding

<222> (1)..(403)

<223> MAr of chromosome 1 genomic contig: 7205509..7205911

<400> 47

tgtatatata tgagtatata tatgtgtata tatgagtata tatatgtgta tatatgagta 240

tatatatatg totatatatg toggtatata tatgtotata tatatgagta tatatgagta tatatgagta 300

tatatatgag tatacatatg tgtatatata tgagcatata tgtgtatata tatgagtata 360

<210> 48

<211> 309

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(309)

<223> MAR of chromosome 1 genomic contig; 7507280..7507588

<400> 48

SEL PCT 012 ST25

tataaa	aatat atattatta tatattatat ataaaaatata tattat	60
atataa	ataaa taaataatat ataatatatt atataattat ttatacataa ttatatata	120
ttatatg	gtaa ttgtacaatt atatataatt atatacaatt atacacataa ttatatacaa	180
ttataca	aatt atatacataa ttatatatat aatatacata attatatatt aattatacaa	240
ttatata	acat aattatatat aattatacaa ttatatacat aattattatg tatattatat	300
tatataa	ata 309	
<210>	• 49	
<211>	516	
<212>	DNA	
<213>	· Homo sapiens	
<220>		
<221>	misc_binding	
<222>	(1)(516)	
<223>	MAR of chromosome 1 genomic contig; 3581085358	600

SEL PCT 012 ST25

aaaatataca taaaaataaa tatatataat ttatat 516

<210> 50

<211> 534

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(534)

<223> MAR of chromosome 1 genomic contig; 3084851..3085384

<400> 50

<210> 51

<211> 583

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<220>

<221> misc binding

<222> (1)..(583)

<223> MAR of chromosome 1 genomic contig; 160087..160669

<400> 51

<210> 52

<211> 314

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(314)

SEL PCT 012.ST25

<223> MAR of chromosome 1 genomic contig; 4350424..4350737

<400> 52

tatgtgtata taaatatatg tatatatgtg tatataaata tatataaata tatgtatata 60

tgtatatata catatattta tatataaata tatgcalata tttatatata aaatatatgc 120

atatatgtat atatataaaa tatatacata tatgtatata tataaaatat atacatatat 180

gtatatatat aaaatatata catatatgta tatatataaa atatatacat atatgtatat 240

<210> 53

<211> 828

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(828)

<223> MAR of chromosome 1 genomic contig; 8443267..8444094

<400> 53

atatataata tatactatag tatatataat atatataata tatactatag tatatataat 120

atatatatat aatatatata atatagtata tataatatat aattatatat aatatataat 240

atagtatata taatatataa tatatatata attatatact ataatatata taatatataa 300

SEL PCT 012.ST25

<210> 54

<211> 573

<212> DNA

<213> Homo sapiens

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<221> misc_binding

<222> (1)..(573)

<223> MAR of chromosome 1 genomic contig; 8703190..8703762

<400> 54

SEL PCT 012 ST25

atatatagaa tatacatata taatatgtat atattatata tatatatata aaaatatata aaaatatata aaaatatata tatatatata aaaatatata tatatatata tatatatata aaaatatatt tatatatata tatatatata aaaatatatt 480 atatatata tatatatata aaaaatatat tatatatata tatatatata taaaaatatat 540 ttatatatta tatataaaaa tatatattata 573

<210> 55

<211> 597

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(597)

<223> MAR of chromosome 1 genomic contig; 8819076..8819672

<400> 55

60 tatatgaaat atacacatat tittatatat ataatatata tattatatat aatatatgca 120 180 240 300 aatatatata atatatata aatatatata ttatatataa aatatatatt atatgtaaaa 360 tatataatat atataatata tatattatat otaaaatata tattatatat aaaatatata 420

SEL PCT 012.ST25

<210> 56

<211> 646

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(646)

<223> MAr of chromosome 1 genomic contig; 759619..760264

<400> 56

<210> 57

<211> 752

SEL PCT 012.ST25

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(752)

<223> MAR of chromosome 1 genomic contig; 1226710..1227461

<400> 57

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<210> 58

<211> 300

<212> DNA

SEL PCT 012.ST25

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(300)

<223> MAR of chromosome 1 genomic contig; 1119049..1119348

<400> 58

taatatacat tttatataat atatgtaata tatattttat atatatgtaa tatatatttt atataatata tgtaatatat attttatata tatgtaatat atattttata taatatatgt 120

<210> 59

<211> 617

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(617)

<223> MAR of chromosome 1 genomic contig; 3603613..3604229

<400> 59

SEL PCT 012.ST25

ataatatata taataaaata tacataatat ataatgtata ataaaatata cataatatat 120 180 240 300 360 420 taaaatatat aatatataat atatataata aaatatatat gatatataat atatataata 480 ataataaaat atatata 617

<210> 60

<211> 674

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(674)

<223> MAR of chromosome 1 genomic contig; 2592460...2593133

<400> 60

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<210> 61

<211> 1694

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1694)

<223> MAR of chromosome 1 genomic contig; 2891680..2893373

<400> 61

SEL PCT 012.ST25

taatatatta ttattattaa tataatatat acatattaat atacatac
ttatatataa tatacatata atataatatg taatattata tataatataa
aatacatatt aataatatat tattaataag ataatatata tgtatctata atatatacat 540
atatgtatat gtatgtatat attatagata tacatgttta tacatgtata tattatagat 600
atatacatgt atatacatgt atatattata gatatataca tgtatatacg tatatattat 660
agatatacat gtatatatgt atatatatta tagatataat atatacaaga atataagaat 720
atatataata taatatataa tacacataat acgtatatat tatatataca tgtatattat 780
atatgtacat atatacatgt atattatata tacatgtata ttatatatac atgcatatta 840
tatatatttt tatatataat atccatgtat attatgtata tttgtgtata ttatatatac 900
atgtatatta tatatacatg catattatat atatttttat atataatatc catatatat
atgtatattt gtgtatatta tatatacaca tatattatat
cacatatatt atatatacat atatattata tatacacata tattatatat acatgtatat 1080
tatatataca cgtatattat atatacacac gtatattata tatacacgta tattatatat 1140
acacacgtat attatatata cacgtatatt atatatacac acgtatatta tatatacacg 1200
tatattatat atacacacgt atattatata tacacgtata ttatatatac acacgtatat 1260
tatatataca cgtatattat atatacacac gtatattata tatacacgta tattatatat 1320
acacacgtat attatatata cacgtatatt atatatacac acgtatatta tatatacatg 1380
tatattatat atacatgtat attatatata cacatgtata ttatatatac atgtatatta 1440
tatatacaca tgtatattat atatgcatgt atattatata tacacatgta tattatatat 1500
acacatgtat attatatata catatatatt atatatacat gtatattatg tatacatata 1560
tattatatat acatgtatat tatagataca tatatattaa atatacatgt atattatgta 1620
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tacatgtata cata 1694

<210> 62

<211> 587

SEL PCT 012 ST25

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(587)

<223> MAR of chromosome 1 genomic contig; 3432560..3433146

<400> 62

<210> 63

<211> 313

<212> DNA

<213> Homo sapiens

<220>

SEL PCT 012.ST25

<221> misc_binding

<222> (1)..(313)

<223> MAR of chromosome 1 genomic contig; 3805392..3805704

<400> 63

tatataatat gtatattatg taatatttta tatagcatat atgtatatta tatataatct 60

tttatatata gtatataata tgtatattat atattatata attatataat tatgtattat 120

tatatggcag tgagctgaga tataatatat attatctata ctatataata tatattatat 240

atactctata ttatatatgt atatattata tataatatat acatatataa tgtgtatata 300

ttatatataa taa

313

<210> 64

<211> 349

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(349)

<223> MAR of chromosome 1 genomic contig; 4521378..4521726

<400> 64

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tataattata tacactatat aatatgtatt tatatataat tatatacact atataatatg 120

tatttatata taattatata cactatataa tatgtattta tatataattg tatacactat 180

SEL PCT 012 ST25

ataatgtata tttatatata attgtataca ctatataatg tatatttatg tataattgta 240 tacactatat aatgtatatt tatgtataat tgtatacact atataatgta tatttatgta 300

taattgtata taccatataa tgtatattta tgtataattg tatatacca

349

<210> 65

<211> 500

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(500)

<223> MAR of chromosome 1 genomic contig; 3240166..3240665

<400> 65

taatatata atatatata tatattata tatatata tatatata tatatatata tatatat

<210> 66

<211> 866

SEL PCT 012.ST25

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(866)

<223> MAR of chromosome 1 genomic contig; 409429..410294

<400> 66

60 aatatataat acatatatta tatatattat atattatata taatatata tacatatatt 180 240 300 420 480 tatgatatat gatatatatg atatatatga tatatgatat atatgatata tatgatatat 600 660 atatgatata tgatatatga tatatattat ataatatata taatatata tatatataat 780 atatataata tataatatat ataata 866

SEL PCT 012 ST25

<211> 335

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(335)

<223> MAR of chromosome 1 genomic contig; 614754..615088

<400> 67

acccaatata tgtgtatata tgtatgtata tatacatata catacataca tatatgtaca 60

tacatatata catacataca tatatatgta catacatata tacatacata catatataca 120

tataacatat atacacacat atatacagat atacatatat acatacatat atacatataa 180

tgtatacata tatgtatata tatattgtta tatat

335

<210> 68

<211> 455

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(455)

<223> MAR of chromosome 1 genomic contig; 1299520..1299974

Seite 66

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4400- 00	
<400> 68 ggatatatat attattagtt gttatattat tatatattat atatattatt atatataata	60
tattatatca tatatattat tatatataat atattatatc atatatat	120
tattatatca tatatattat tatatataat atatattata tatattat	180
atattatata tattattatg tataatatat atattatata ttatttat	240
tatataataa tatataatta attatacata tatacatata taagtataca tataatata	at 300
ttatatagta tatataaata tatatacaat atatttatat attatatatt atatataaat	360
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gatatataat atatatcata tatgatatat aacat 455	
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<211> 404	
<212> DNA	
<213> Homo sapiens	
<220>	
<221> misc_binding	
<222> (1)(404)	
<223> MAR of chromosome 1 genomic contig; 1970778197	1181
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atatgcatta tatattatat attgcatata atatgcatta tatattatat	240

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atatgcatta tatattata aatatataca catataatat atataattta 300 tatatattta catttattat atattatta tatatatta tatatatta tatatatta tatatatta tatatatata tatatatata tatatatata tatatata 404

<210> 70

<211> 605

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(605)

<223> MAR of chromosome 1 genomic contig; 3562918..3563522

<400> 70

60 120 acatataata tatatgatat ataatacata tataatatat atgatatata atacatatat 180 aatatatatt atatataata catatataat atatattata tataatacat atataatata 240 ataatacata tataatatat attatataat acatgtatat aatatatat atatataata 360 catatatatt atataataca tgtatataat atatattata tataatacat atatattata 420 aatattatat ataatacata tattatatat aatataaata tatataatac atatataata 540 cacatattat atataataca tatattatat ataatatata tattatatat aatatatat 600 taata 605

SEL PCT 012.ST25

<210> 71

<211> 317

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(317)

<223> MAR of chromosome 1 genomic contig; 189743..190059

<400> 71

tattttttat atttatatat tatatatatt tttatatgta atatattata tataaaatta 60

tataatttta ctacatataa tatataaaat tatataattt tactacatat aatatataaa 120

tgtatataaa atatataata tataatatat ttatagacaa taatatataa tataatatat 300

aaaattttat atataaa

317

<210> 72

<211> 522

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(522)

SEL PCT 012.ST25

<223> MAR of chromosome 1 genomic contig; 229111..229632

<210> 73

<211> 1110

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1110)

<223> MAR of chromosome 1 genomic contig; 1138030..1139139

<400> 73

SEL PCT 012.ST25

attatatgta tattatgtat acataatata ttatatatta tatgtatatt atgtatacat	180
aatatattat atattatatg tatattatgt atacataata tattatatat tatatgtata	240
ttatgtatac ataatatatt atatattata tgtatattat gtatacataa tatattatat	300
attatatgta tattatgtat acataatata ttatatatta tatgtatatt atgtatacat	360
aatatattat atattatatg tatattatgt atacataata tattatatat tatatgtata	420
ttatgtatac ataatatatt atatattata tgtatattat gtatacataa tatattatat	480
attatatgta tattatgtat acataatatt tatatattat atgtatatta tgtatacata	540
atatattata tattatatgt atattatgta tacataatat gtacacataa tatttatata	600
ttatatgtat attatgtata cataatattt atatattata tgtatattat gtatacataa	660
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gtatacataa tatttatata ttatatgtat attatgtata cataatatat tatatattat	780
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atacataata tattatatat tatatgtata ttatgtatac ataatatatt atatattata	960
tgtatattat gtatacataa tatattatat attatatatg tatattatgt atacataata	1020
tattatatat tatatatgta tattatgtat tatattatat attatgtata ttatagatta 1	080
tgtatgcata cataatatgt attgtatatt 1110	

<210> 74

<211> 521

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(521)

SEL PCT 012.ST25

<223> MAR of chromosome 1 genomic contig; 2863407..2863927

<210> 75

<211> 560

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(560)

<223> MAR of chromosome 1 genomic contig; 5712303..5712869

<400> 75 atataattat atatatata tatattata ataattata attatata atgtataatt 60 atatattata tataatatat ataaatata atatttitta tataaatata ttatatattt 120

SEL PCT 012.ST25

<210> 76

<211> 479

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(479)

<223> MAR of chromosome 1 genomic contig; 8578812..8579290

<400> 76

SEL PCT 012 ST25

<210> 77

<211> 477

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(477)

<223> MAR of chromosome 1 genomic contig; 8579294..8579770

<400> 77

<210> 78

<211> 331

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<220>	
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<222> (1)(331)	
<223> MAR of chromosome 1 genomic contig; 85800248580	354
<400> 78 actatatgtt atatacataa gatatagtat ataccatata ttatatacat tatatatagt	60
assaciate italiatata galalagia alaccalala italiataca italiataiagi	60
gtatactata tataatgtat ataatatata gtatatatac actatatata ctatgtatat	120
atacactata tatactatgt atatatacac tatatatact atgtatatat acactatata	180
tactatgtat atatacacta tatatactat gtatatatac actatatata ctatgtatat	240
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tactgtatat gttatagtgt atatatagta t 331	
<210> 79	
2044 440	
<211> 410	
<212> DNA	
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<220>

<221> misc_binding

<222> (1)..(410)

<223> MAR of chromosome 1 genomic contig; 8580705..8581114

<400> 79 tatagtotat attatataca gtotatataa tatatagtat atactatata tacttttoot 60

SEL PCT 012 ST25

cattotgact atatactata tatatactat atatagtata tgtagtgtat atatacacca 120 tatatactat atatagtata cataccatat atagtatact atacatacca tatatagtat 180 acataccgta tatagtatac tatacttacc atatatagta tacatactat atatactat atatactat tatacactat atatacatat 1240 totggtgtat atatacacta tatatactat atatactat atatactat atatagtat gtacactatt 1360 gtagactata tataatatag actatgtgta gagtatatat actatatata 1410

<210> 80

<211> 433

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(433)

<223> MAR of chromosome 1 genomic contig; 12979167..12979599

SEL PCT 012.ST25

<210> 81

<211> 385

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(385)

<223> MAR of chromosome 1 genomic contig; 16336644..16337028

<400> 81

tttatataaa tatctatata aataaatata taaatatata aatataaata tatataaata 60

tataaataaa tatataaata tatataaata taaatatata tataactatg aatttatatt 120

taaatatata totatatatg aatatatato tataggaata taaatatata totatataaa 300

tataaatata aatatatata taaat

385

<210> 82

<211> 363

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

SEL PCT 012.ST25

<222> (1)..(363)

<223> MAR of chromosome 1 genomic contig; 20624448..20624810

<400> 82

tatatatata gittatata tatitatata tatagitata tatatatitt tatatagita tatatatata gitatatata gitatatata tatagitata tatatagita tatatatagit tatatatatagi tatatatata tatagitata tatagitata tatatagita tatatatagi tatatatata tatagitata tatatagitata tatatagitata tatagitata tatatagitata tatagitata tatatagitata tatatagitata tatagitata tatagitata gitatatata gitatatata tatagitata tatatatagit tatatatata gitatatata gitatata gi

<210> 83

<211> 310

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(310)

<223> MAR of chromosome 1 genomic contig; 566025..566334

<400> 83

SEL PCT 012.ST25

atattgtata tataatatat atattgtata tattatatat agtatatatt atatatagta 300

tatataatat

310

<210> 84

<211> 1236

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(1236)

<223> MAR of chromosome 1 genomic contig; 1171429..1172664

<400> 84

aaagtattat atgtattata tgtatatgta ttatatatta catatgtatt atatataata 60

tatattatat attattatat attatatatt attatatat attatataa tgtattatat 120

attatatagt atatatagta tatataatgt attatatatt atatagtata tatagtatat 180

ataatgtatt atatatagta tatataatgt attatatagt atatatacta tataatgtat 240

tacatattat gtatagtata tgtaatgtat tatatattat atagtatatg taatgtatta 300

tgtattatat aacatatata atatatatga tgtattatat agcatgtata gtatatatga 420

tgtattatat agcatgtata gtatatatga tgtattatat atagcatgta tagtatatat 480

gatgtattat atatagcatg tatagtatat atgatgtatt atatatagca tgtatagtat 540

atatgatgta ttatatatag catgtatagt atatatgatg tattatatat agcatgtata 600

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SEL PCT 012.ST25

<210> 85

<211> 309

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(309)

<223> MAR of chromosome 1 genomic contig; 1925173..1925481

<400> 85

SEL PCT 012.ST25

aatgtatat

309

<210> 86

<211> 312

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(312)

<223> MAR of chromosome 1 genomic contig; 4396756..4397067

<400> 86

cacagigitat atatagiata tatacigitat atatacigig tatatacaci gitatatacac 60 agrigitatata cagitatatat actatatata cacigigitat atatagitata tataaattot 120

aggaatatat atactatata tatactatat atataaattc taggaatata tacacactat 180

acactatata tacacgagat atataacata tacactatat actatacata acatatatac 300

tatatatact at

312

<210> 87

<211> 398

<212> DNA

<213> Homo sapiens

<220>

SEL PCT 012.ST25

<221>	misc_	_binding
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<222> (1)..(398)

<223> MAR of chromosome 1 genomic contig; 56057..56454

<210> 88

<211> 391

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(391)

<223> MAR of chromosome 1 genomic contig; 56984..57374

SEL PCT 012.ST25

180 taatacataa tatataaatt atattatatt atttatatat aatgtatgcc atataattta 240 tatataatgc attatatata atttatatat aatgcattaa atataaatta tatataatgc 300

attatatata attatatata atgcattata tataatttat atttaatata taaatttata 360

tttaatatat ttatatatta tatataataa a

391

60

<210> 89

<211> 309

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(309)

<223> MAR of chromosome 1 genomic contig; 469547..469855

<400> 89

atatgttata tataatatat atgttatata tacgttatat gttatatata tgttatatat 120 180 tatatattat atataatata taatatatgt gatatataat ataaaatata tgtgatatat 300

attatatat

<210> 90

<211> 441

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(441)

<223> MAR of chromosome 1 genomic contig; 546190..546630

<400> 90

atacacaaca tatgtgtata tatatagtat atatacacaa catatgtgta tatatatagt

atatatacac aatatatgtg tatatatata gtatatatac acaatatatg tgtatatata 120

gtataaatat atactatata tagtatatat agtataaata tatactatat atagtatata 180

catagtataa atatatacta tatatagtat atacatagta taaatatata ctatatatag 240

tatatacata gtataaatat atactatata tagtatatac atagtataaa tatatactat 300

atatagtata tacatagtat aaatatatac tatatatagt atatacatag tataaatata 360

tactatatat agtatataca tagtataaat atatactata tatagtatat acatagtata 420

aatatatact atatatagta t

441

<210> 91

<211> 1367

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1367)

<223> MAR of chromosome 1 genomic contig; 124643..126009

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atattatat gatatataat atatataata ttatatata
attatataat attatatatg atatatatta tatatattat atatgatata taatatatat
aatattatat atgatattat atatcatata taatatataa aatattatat atgatatata 180
atatatataa tattatatat attatatata ttatatatca tatataatat tctaaatata 240
taatattata tgatatataa gattatatac attatataa atatataata ttatatatga 300
tatataatat tatatacatt atatataata tataatgtat ataatattat atattatata 360
tttatattat atacaatgta tataatatta tatatcatat atatttatat tatacaat 420
distance that a total and a to
atattletet tetere en tit i de en en en en
gtatataata tatattatat atatttatat tatatacaat gtatacaata ttatatatta 600
tatattatat atttatatta tatacaatgt atatattata tattatatat ttatattata
tacaatgtat atattatata ttatatattt atattatata caatgtatat attatatatt 720
atatatttat attatataca atgtatatat tatatattat atatttatat tatatacaat 780
gtatatatta tatattatat atttatatta tatataatgt atgtaatatt atatattata 840
tatttatatt atatataatg tatgtaatat tatatattat atatttatat tatatata
gtatgtaata ttatatatta tatatttata ttatatata
atatatttat attatatata atgtatgtaa tattatatat tatatattta tattatatat 1020
a atgtatgta atattatata ttatatattt atattatata taatgtatgt
attatatatt tatattatat ataatgtatg taatattata tattatatat ttatattata 1140
tataatgtat gtaatattat atattatata tttatattat atataatgta tgtaatatta 1200
tatattatat atttatatta tatataatgt atataatatt atatattata tatttatatt 1260
gtatataata ttatatatta tatatttata ttgtatataa tatatattat atatttatat 1320
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SEL PCT 012.ST25

<210> 92

<211> 458

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(458)

<223> MAR of chromosome 1 genomic contig; 58908..59365

<400> 92

<210> 93

<211> 330

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<221> misc binding

<222> (1)..(330)

<223> MAR of chromosome 1 genomic contig; 306867..307196

<400> 93

tatgatatct atctatatat atcatatata

330

<210> 94

<211> 353

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(353)

<223> MAR of chromosome 1 genomic contig; 636899..637251

<400> 94

tatgtataca tatacacata tacgtatata tatacatata tacacatata cgtatatata 60 tacgtataca tacatatgta tatgtatacg tatacacaca tatgtatatg tatacgtata 120

cacacatata cgtatatatg tatacgtata cacacatata cgtatatgta tacatatata 180

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353

tototacata tacotatata cotatatota tacatatata cotttatota tatatacota 240 tatacgtata tatgtatatg tatacatata tacatatatg tgtatatacg tatatacgta 300

tatgtgtata tatacaatat acatacatgc acatatatgt gtatatgcac ata

<210> 95

<211> 345

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(345)

<223> MAR of chromosome 1 genomic contig; 1435510..1435854

<400> 95

atcatatata ttatatatca tatatatgat atataaaaat tatatatcat atatatgata 60

taatatata aaattatata tatcatatat atgatatata atttatatat catatatatg atatatata tatatatti atatataata tattatatat tatataatat gtaatatata 240

aatatagaat attatatatt atatattaca tattatataa tatat 345

<210> 96

<211> 521

<212> DNA

<213> Homo sapiens

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<220>	
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<222> (1)(521)	
<223> MAR of chromosome 1 genomic contig; 3969540	215
<400> 96 tatatatata atagatatta tatatctatt atatatctat tatatatata atagatat	ita 60
tatatctatt atatataa tagatattat atatctatta tatatataat agatatta	ita 120
tatctattat atataatata tatctattat atattatata tctattatat ataatatata	a 180
tctattatat atattatata tctattatat atataataga tattatatat ctattatat	240
taatatatat ctattatata ttatatatct attatatata	300
tgtatctatt atatataata tatatctatt atatatata	a 360
tatattatat atctattata tataatatat atctattata tatattatat atctattata	420
tatattatat atctattata tataatatat atctattata tatattatat atctattata	480
tataatatat attatatata tattatatat tgtatatcta t 52°	I
<210> 97	
<211> 484	
<212> DNA	
<213> Homo sapiens	
<220>	
<221> misc_binding	
<222> (1)(484)	

<223> MAR of chromosome 1 genomic contig; 1286007..1286490

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<400> 97 atatcatata tattatatat catatatatg atatataaaa attatatatc atatatatga	60
tatatataaa ttatatatat catatataat atatataata tattatatat ataaattata	120
tataatatta tatataaatt atatatcaca tatatgacat ataaattata tatcacatat	180
atgatatata atttatat at cacatatatg atatataatt tatatatcat atatatgata	240
tataatttat atatcatata tatgatatat aatttatata tcatatatat gatatatata 3	00
atatattatt talatataat atattatata ttatataata tgtaatatat attatatatt 360	o
atataatatg taatatatat tatatattac atattatatt	0
aatatatata atattatata atatagaata ttatatatta tatattacat attatataat 4	480
atat 484	

<210> 98

<211> 244

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(244)

<223> MAR of chromosome 1 genomic contig; 73556..73879

<400> 98

aata

<210> 99

<211> 463

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(463)

<223> MAR of chromosome 1 genomic contig; 179038..179500

<400> 99

<210> 100

<211> 390

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25 <220> <221> misc binding <222> (1)..(390) <223> MAR of chromosome 1 genomic contig; 55617..56006 <400> 100 tgtataatat atatacttta tatataatat atatacttta tatatact atatactaat 60 120 atatatacta atatatatta tatatacttt atataatata tactaatata tataatatat 180 atactttata tataatatat actaatatat ataatgtata tactttatat ataatatata 240 atatataa tatatactta tatattatat atgcttatat ataatatata cactaatata 360 taatatatat actitatata tiatatitia 390 <210> 101 <211> 582 <212> DNA <213> Homo sapiens <220> <221> misc binding

<222> (1)..(582)

<223> MAR of chromosome 2 genomic contig; 1157405...1157986

<400> 101 tgtatatgta tatatacaca tacgcacata tatgtatatg tatatataca catacgcaca

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tatatgtata tgtatatata cacatacgca catatatgta tatgtatatg tatatgtata	120
tatacacata tacacatata tgtatatgta tatatacaca tatacacata tatgtatat	g 180
tatatataca catatacaca tatatgtata tgtatatata cacatacaca tatatgtata	a 240
tgtatatgta tatatacaca tacacatata tgtatatgta tatgtatata tacacatata	300
cacatatata catatatgta tacatatatg tgtatatata tacacatata tatacatata	360
tgtatacata tatgtgtata tatacacata tatatacata tatacatata catatatat	420
tgtatgtata tatacacata tacatatata tgtatatgtg tatatatatt agacagatat	480
atatgtacat atacatatat atgtatatgt atatgtatat gtatatgtat atgtatatgt	540
atatgcatat ataatataca tatacatata tgtatatgta ta 582	

<210> 102

<211> 322

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(322)

<223> MAR of chromosome 2 genomic contig; 1858638..1858959

<400> 102

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240

300

360

480

540

600

660

420

ccatatatat acaccatata ta

<210> 103

<211> 914

<212> DNA

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<221> misc binding

<222> (1)..(914)

<400> 103

<223> MAR of chromosome 2 genomic contig; 5712196..5713109

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tatattctat atatattcta tatatataga atatatatat aaaacatata ttctatatat 120 aaaatatata tictatatat ataaaatata tattotatat atatagaatg tatataaaat atatattcta tatataga atgtatataa aatatatatt ctatatata agaatgtata taaaatatat attotatata tatagaatgt atataaaata tatattotat atatagaa tatatataac atatataga aatatatata aaatatatat aaatacatat ttctatatat

aaattatata taaatatata ttcatatata taatatata aaatattat ttcatatata

aaatatattt aaatatatat ttotatatag aatatatatt otatatata aatatatata

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tatatatact atatatacaa tatatattat atataaaata tatatacaat atatattcta 840 tatattaata tatagaatat atattaacat atatttcaat atattaatat atgaaatata 900

tataaatatt tcat

914

<210> 104

<211> 370

<212> DNA

<213> Homo sapiens

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<222> (1)..(370)

<223> MAR of chromosome 2 genomic contig; 5713613..5713982

<400> 104

<210> 105

<211> 442

<212> DNA

<213> Homo sapiens

<221> misc binding

<222> (1)..(442)

<223> MAR of chromosome 2 genomic contig; 7481647..7482088

<210> 106

<211> 338

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(338)

<223> MAR of chromosome 2 genomic contig; 9594557..9594894

PCT/EP2004/011974 WO 2005/040377

SEL PCT 012.ST25

<400> 106 tatataaata tataccatat atataaatat atatattcca tatataaata tatatattcc	60
atatatataa atatatata teeatatata aatatatat	120
atataaatat atatattcca tatatataaa tatatata	180
aatatatata tattocatat ataaaaatat atatatatto catatataaa aatatatata	240
tattccatat atataaatat atatatattc catatatat	300
atataaatat atatatatc catatatata aatatata 338	

<210> 107

<211> 364

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(364)

<223> MAR of chromosome 2 genomic contig; 10519720..10520083

<400> 107 ttatatatat ttataataat atatataagc tatatatatt tatatataat atattatata 60 tattagctat atatatttat ataataatat attatatatt agctatatat atttatatat 120 aataatatat ataagctata tatttatata tattatatat tagctatata tatttatata 180 taatatatta tatattagot atatattat atataataaa taatatatat attagotata 240 gctatatata tttatatata ataatatatt atatattagc tatatatatt tatatataat 360 atat 364

Seite 97

<210> 108

<211> 342

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(342)

<223> MAR of chromosome 2 genomic contig; 11481943..11482284

<400> 108

gtaatatata tataatatat atgtaatata tatattatat atatgtaata tatatcatat 300

atatgtaata tatatcatat atatgtaata tatatcatat at

342

<210> 109

<211> 415

<212> DNA

<213> Homo sapiens

<220>

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<222> (1)..(415)

SEL PCT 012.ST25

<223> MAR of chromosome 2 genomic contig; 13499598..13500012

<210> 110

<211> 330

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(330)

<223> MAR of chromosome 2 genomic contig; 16370976..16371305

<400> 110

catttacata tgtatgtata agtatgtata ttacatactt atacatacat acttataaat 60
atataagtat aatacataca tacttataaa tatataagta taatacatac atacttatac 120
atatataagt ataatacata catacttata catacttata tatataag tataatacat acatacttat 180
acatatataa gtataataca tacatactta tacatactta tacatatata gtataataca acatacttat 240

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acatatataa gtataataca tacatactta tacatatata agtataatac ata cttatta 300

catatgtata taagtatatt acatacttat

330

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<211> 702

<212> DNA

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<221> misc_binding

<222> (1)..(702)

<223> MAR of chromosome 2 genomic contig; 626641..627342

<400> 111

180 300 360 420 540 tacatatata ttttatatat atataatata tattttatat at 702

Seite 100

<210> 112

<211> 679

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(679)

<223> MAR of chromosome 2 genomic contig; 3196047..3196725

<400> 112

atatattata tattoatata toataaatat atatattata tattoatata ttatatatot 60 atatattat atattcatat attatatat tatattatat tatattatat 120 ctatttatat attcatatat tatatatcta tatattttat atattcgtat attatatatc 180 tatatattat atattcgtat attatatatc tatatattat gtattcatat atatctatat 240 attatatata ttcatatata ttataaatta tattcatata gtatatatct attataaatg 300 tatattcata tagtatatat ctatatatta taaatataca tatattatat atttatatat 360 tatatattca tatagatcta tatattatat atattcatat atgaatatat atattatatg 420 tatatatatt ataaatatat ttatatagta tagatattat atagtatatg catatttata 480 ttataaataa tttacatagt atatgtatat ttataaatta tatatattta catattacat 540 gtatatttat atattataaa tacatattta catattataa atatattat atattatgaa 600 tataatttat atattattac atatttacat atatgcatag ttatatatta taaatatgca 660 tttatgtaaa tatatattt 679

<210> 113

<211> 728

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(728)

<223> MAR of chromosome 2 genomic contig; 3196778..3197505

<400> 113

tacataaata tatatttaca atatgtaaat atctgatatg taaatatgta tttataatat 60 ataaatatac atataatatg taaatatata aatatacata tactatgtaa atatatgtta 120 tatatacata tactatataa atatagaata tataaatata catatactat ataaatatgt 180 240 aatatataaa tatatactat ataaatatac atatactata taaatgtatt tataatatat aaatatacat atactatata aattcatata tgaatatata atatataaat atatataata 300 tatgaatata tactcatata taaatatata tgaatatata tttataatat atagatataa 360 agatatatac catatgaata tatattatac actatatgaa tatatattta taatatataa 480 atagatatat actatatgaa tatataatat atatactcta tgaatatata atatatatac 540 tatatgaata tattatatac tgtatgaata tataatatat agatgtatac tatatgaata 600 tataatatat agatatatat actatatgaa tatatataat atatagatat atactatatg 660 aatatatatg atatatagat atatactata tgaatatata atatatagat atatattat 720 728 gatatatg

<210> 114

<211> 413

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(413)

<223> MAR of chromosome 2 genomic contig; 2560638..2561050

<400> 114

atataaatat atattatat attttatata aatatatata tttatatatt tttatataaa 60

tatatatatt tatataatt tatataaata tatatattta tatatattta tataaatata 120

taaatatata tatttatata aatatataaa atatataaat atatttatat aaatatataa 180

aatatataaa tatatttata taaatatata aaatatataa atatatttat atataaatat 240

ataaaatata taaatatott tatatataaa tatataaaat atataaaatat otttatatat 300

aaatatataa aatatataaa tatatttata tataaatata taaaatatat aaatatattt 360

413

<210> 115

<211> 361

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(361)

<223> MAR of chromosome 2 genomic contig; 4965309..4965669

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<400> 115 tatacgtata tatacatata tatacgtata tatatacata tatatacgt	a tatatacata	60
tgtatatatg tgtgtacatg tatatatata catatgtaca tatatatgta	cacatatata	120
tatacatata tatgtacaca tatacatata tatgtacaca tatacata	ta catatatatg	180
tacacatata tatacatata tatgtacaca catatatata catatata	tg tacacacata	240
tatacgtata tatgtacaca catatatacg tatatatatg tacacaca	ita tatacgtata	300
tatatgtaca cacatatata tacgtatata tatgtacaca tatatatat	a cgtatatata	360
t 361		
.040: 440		
<210> 116		
4044s 20E		

<211> 32

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(325)

<223> MAR of chromosome 2 genomic contig; 5258150..5258474

<400> 116

<210> 117

<211> 1508

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1508)

<223> MAR of chromosome 2 genomic contig; 6057499..6059006

<400> 117

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attacataat atagtataat atataacata tyttatatat tacataatat agtataatat 900
ataacatatg ttatatatta cataatatag tataatatat aacatatgtt atatataca 960
taatatagta taatatataa catatgttat atatacata atatagtata atatataaca 1020
tatgttatat attacataat atagtataat atataacata tyttatatat tacataatat 1080
agtataatat ataacatatg ttatatatta cataatatag tataatatat aacatatgtt 1140
atatattaca taatatagta taatatataa catgttatat attacataat atagtataat 1200
atataacata tgctatatat tacataatat agtataatat atatgttata tattacataa 1260
tatagtataa tataacata atgttatata tacatatata tatagtataa 1320
atattatata atatagtata atatataag tatgttatat attatataata tatagtata 1380
atataacatg ttatatata tataatatag tataatata tatgttatat tatataata
atataacatg ttatatata tataatatag tataatata tatgttatat tatataata
tataacatg ttatatata tataatatag tataatata tatgttatat tatgttatat
tataatata 1500
attatata 1508

<210> 118

<211> 415

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(415)

<223> MAR of chromosome 2 genomic contig; 7996866..7997280

<400> 118

caattatata atatacatat tatataattg tataaattat acaatcatat aattatatta 60

tatataatat acatataata taattatata taattatata attttataat ataattatat 120

SEL PCT 012.ST25

<210> 119

<211> 526

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(526)

<223> MAR of chromosome 2 genomic contig; 8300930..8301455

tatatcatat gatatattat acaatatatc atataatatg atatattata tgatatattg

<400> 119

<21	0.	2	^

<211> 402

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(402)

<223> MAR of chromosome 2 genomic contig; 8576553..8576954

<400> 120

atgtatatta tatacaatat agtatatcat atatagtata tattatatag taatgtatta 60

tatatattat atatgataca tatactatat aatatgctat atattatact atataatatg 180 ctatatatta tactatataa tatgctatat attatactat ataatatgct atatattata 240

ctatataata tgctatatat tatactatat aatatactat ataatatgct atatattata 300

ctatataata tactatata tatactatat aatatactat ataacatact atatattata 360

tatgatacat atactatatt acatatataa tatatatata ta 402

<210> 121

<211> 477

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

SEL PCT 012.ST25

477

<222> (1)..(477)

<223> MAR of chromosome 2 genomic contig; 8785649..8786125

<400> 121
tatttatata tatatttata tatatattta tatatattta tatatattta tatatatta tatatatta tatatatta tatatatta tatatatta tatatatta tatatatta tatatatta tatatata tatatatta tatatata tatatata tatatata tatatata tatatata tatatata tatatata tatatatata tatatatata

tatatatatt tatatatata tttatatata tatatttata tatatatta tatatat

<210> 122

<211> 773

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(773)

<223> MAR of chromosome 2 genomic contig; 10064737..10065509

<400> 122

SEL PCT 012.ST25

<210> 123

<211> 1554

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(1554)

<223> MAR of chromosome 2 genomic contig; 1039775..1041328

<400> 123

ataatatatt aaatgtatat ataatatatt aaatataaat atatttataa tatataaata 60
tttatataaa tataaaatat atattaaata taaatatata taaaatatat attaaatata 120

taaaatataa atatatatta aatatatat aaatatata aatataaata tatattaaat 180

SEL PCT 012.ST25

atattttaaa tatataaaat ataaatatat attaaatata ttttaaatat attaaatata 240
aatatatatt aaatatattt taaatatatt aaatataaat acatatatta aatatatat
atatatataa aatatataaa atataaatat atattaaata tatataaaat atatatgtta 360
aatatataaa agatatataa aatataaata tatattaaat atatataaaa tatatatata 420
ttaaatatat atattaaata taaatatata taaaatataa atatatgtat taaatatata 480
tattaaatat aaatatatgt attaaatata tattaaatat gaatatatgt attaaatata 540
tattaaatat aaatatatgt attatatata tagaatataa atatatgtat taaatatagt 600
atattaaata taaatatata taaaatatat attaaatatg aatatatat
attaaaaata tatataatat aaatatatat aaaatatata tattaaaaat atatataata
taaatatata taaaatatat atattaaaaa tatatataaa atatatatat taaaaatata 780
tataaaatat atatattaaa aatatatata aaatatatat attaaaaata tatattaaat 840
ataaatatat atattaaaaa tatatattaa atataactat atattaaata tatattaaat 900
ataactatat attaaatata tattaaatat aactatatat taaatatata ttaaatataa 960
ctatatatta aatatatatt aaatataact atatattaaa tatatattaa atataactat 1020
atattaaata tatattaaat ataactatat attaaatata tattaaatat aactatatat 1080
taaatatata tgaaatataa ctatatatta aatatatatt aaatataact atatgtatta 1140
aatataaata tatgtottaa atatatatta aatataaata tatgtattaa atatatat
aatataaata tgtgtattaa atatatatta aatataaata tgtgtattaa atatatat
aatataaata tgtgtattaa atatatatta aatataaata tgtgtattaa atatctatat 1320
aaatataaa tatatgtatt aaatatatat taaatataaa tatatattaa atatatatat 1380
aaatataaa tatatattaa atataaatat atatattaaa tatatatatt aaatataaat 1440
atatataaaa tatatatatt aaatataaat ataaatataa aatatatatt aaatataaat 1500
acatatatta aatatatota ttaaatatat atataaaata tatotattaa atat 1554

<210> 124

<211> 650

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(650)

<223> MAR of chromosome 2 genomic contig; 3944813..3945462

catgatatat tatgtataat atatattata gattacatat aaattatata tataatatat

<400> 124

tattacatat atattatgta atataatatg caatatgtta catatataat atatatgtat 540 tatatagtat atatactata gtatatataa aatatatgct ataatatata tittatatat 600

tatataatac atataatgta tcatatatta tatataatat attttataat

<210> 125

<211> 441

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(441)

<223> MAR of chromosome 2 genomic contig; 5314265..5314705

<400> 125

<210> 126

<211> 1169

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1169)

<223> MAR of chromosome 2 genomic contig; 5953971..5955139

<400> 126

atgtattcat attatatatt tatatataaa taatatacat tcatattata tatttatata 60)
taaataatat atattcatat tatatattta tatataaata tataatatat ttatgtataa 12	20
ataatatata tattcatatt atatatttct atataaataa	0
atttatatat aaatatataa tatatttata tataaatata taatatattt atatataata	40
tatatattca tattatatat ttatatataa atatataata tatttatata taaataat	0
atatattcat attatatatt tatatataaa taatatata tcatattata tatttatata 360	,
taaataatat atattcatat tatatactta tatataaata atatatat	20
cttatatata aataatata attcatatta tatatttata taaaaataat atatattcat 48	30
attatatatt tatatataat atatatattc atattatata tttatatatt ctatatattc 540	
atattatata tttatatata aataatgtat attcatatta tatatttata tataaataat 600	J
gtatattcat attatatatt tatatataaa tatatattca tattatatat ttatatata	
atatatattc atattatata tttatatata aatatatat	
aatatatat ttcatattat atttatatat aaatatatat	
ataatatat tattcatatt atatatttat atataatata tatattcata ttatatattt 840	
atatataaat aatatatat ttcatattat atatttatat ataaataa	0
ttatatattt atatataaat aatgtatatt catattatat atttatatat aaatatatat 960	
attcatatta tatatttgta tataaatata tattcatatt atatatttgt atatatattc 1020	
atatatattt atatataaat atataatatt catattatat ataaaatatat atattcatat 108	0
tatatattta tatatataaa taatatatat toatattatt tatatata	o
attcatatta tttatatata taaataata 1169	

<210> 127

<211> 653

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<220	>
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<221> misc binding

<222> (1)..(653)

<223> MAR of chromosome 2 genomic contig; 6427669..6428321

<400> 127

60 tatatatgta tacatatatg tatatatgtg tatatatgta tacatatatg tatatatgtg tatatatgta tacatatatg tatatatgta tatatatgta tacatatatg tatatatgta 120 tatatatgta tacatatatg tatatatgtg tatatatgta tacatatatg tatatatgtg 180 tatatatgta tacatatatg tatatatgtg tatatatgta tacatatatg tatacatgtg 240 tacatgtgta tacatatatg tatacatgtg tacatgtgta tacatatatg tatacatgtg 300 360 tacatgtgta tacatatatg tatatatgtg tatacatata tgtatatatg tgtatatatg tatacatata totatataag totatatatg totatatgta tataagtgta tatatgtgta 420 tatgtatata agtgtatata tgtgtatatg tatataagtg tatatatgtg tatatatgta 480 tacatatatg tatatatgtg tatatatgtg tatatgtata taagtgtata tatgtgtata 540 tatgtataca tatatatgtg tatatatgta tacatatatg tatatatgtg tatatatgta 600 653 tacatatatg taaatatgtg tatatatgtg tatatgtata taagtgtata tat

<210> 128

<211> 414

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(414)

SEL PCT 012.ST25

<223> MAR of chromosome 2 genomic contig; 10890453..10890866

<210> 129

<211> 496

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(496)

<223> MAR of chromosome 2 genomic contig; 13952568..13953063

<400> 129

SEL PCT 012.ST25

<210> 130

<211> 317

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(317)

<223> MAR of chromosome 2 genomic contig; 16942865..16943181

<400> 130

totoctagda gitatatata tatatatgig tatatatata tatoctagta gatatatata 60 tatatatato otagtagata tatatatata tatatoctag tagatatata tatatatata 120 toctagtagt tatatatata tatatatoct aacagitata tatatatata toctagtagt tatatatata tatatatoctag tagitatata tatatatata toctagtagt tatatatata 240 tatatoctag tagitatata tatatatato ctagtagita tatatatata tatatatata 300

tataatatat atataat

317

<210> 131

<211> 464

<212> DNA

PCT/EP2004/011974 WO 2005/040377

SEL PCT 012.ST25

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(464)

<223> MAR of chromosome 2 genomic contig; 17217049..17217512

<400> 131

acatactata tatatacaca tactatatat actatataca gtatatagta tacatatact 60

atacatatac atatactata catatacata tacatatact aagtatacgt atatacagta 120

catagtatat gtatactata tagtatgtat atatagcata tagtatgcgt atactctata 180

tagcatatag tatgcatata cgctatatag catatagtat gcatatacta tatatagtat 240

agtatgcgta tactatatat atagtataga gtatgcgtat actatatat tagtatagag 360

tatgcgtata ciatatatat agtatagagt atgcgtatac tatatatata gtatagagta 420

tgcgtatact atatatatag tatagagtat gtatatatat agta

464

<210> 132

<211> 430

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(430)

<223> MAR of chromosome 2 genomic contig; 19647266..19647695

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<400> 132 tgtaaatata tgtaaatata tatttatatt atatattata taaaaatata atatataata
tataatatat aaactatata ttaatataat atatataaac tattatataa atacatatta 120
aatatattat attittaata titatatatt aaatataata tatatttaat attitatatat 180
taaatatata atatattiaa tatttatata atatatagca tattttatat ttatattata
tataacattt tatatttata tttatattta tatatattta atttatattt atattat
tatatttata ttatatataa cataattata tatatttica tattgtatat aataaagaaa 360
tgtatatttg ttatatataa tatatattat ataatttatt atatattat
tatataatat 430

<210> 133

<211> 2131

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(2131)

<223> MAR of chromosome 2 genomic contig; 20481223..20483353

<400> 133

atatttaata taaatatott tatatttaat atatatttaa tataaatato ttitatattta 120 atatatattt atataaaat atatatttat atttaatata tattaatatt taatataogt 180 ttatattitaa tatatattito tatataaata tattatatti aacalatatt tatatataaa 240

tatatataaa tatatttata tttaatatat atttatataa atatatttt atataaatat

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tatatttata tttaatatat ttacatataa atatatttat atotaatata tttacatata 300 aatatattta tatttaatat atatgcatat gtaaatatat ttatatttaa taatatttat 360 atataaatat atttatattt aataatattt atatataaat atatttatat ttaatatata 420 480 tattatatat aaacatatat ttatatttaa tatatattat atataaacat atatttatat ttaatatata ttatatataa acatatattt atatttaata tatatttata tttaatatat 600 tatatataaa catatattta tatttaatat atatttatat taaatatata ttatatataa 660 acatatattt atatttaata tatatttata ttaaatatat atttatattt aatatatata 720 tattaaatat atatttatat ttaatatata tttatattaa atatatattt atattaaata 780 tatttatatt taatatatat ttatattaaa tatatataa atatttaata tatatttata tttaatatat acatatatat ttatatttaa tatatacata tatatttata tttaatatat 900 acatatatat ttatatttaa tatatacata tatatttata tttaatatat aaatttatat 960 tttatatata taaaaatata tatttatatt taatatatat aaatatatat ttatatttaa 1020 tatatatatt tatattoaat atatacataa atatatattt atatttaata tataaacata 1080 tatttatatt tatatattaa atatatattt atatttaata tataaatata tatttatatt 1140 tatttaatat atttatgtgt attaatatat ttatatttaa tatatttata tattaatata 1260 tttatatttt atatttatat attaatatat ttatatttta tatttatatt ttatatattt 1320 tatttatata ttaataaatt tatattttat acacttatat aaatatattt atatttata 1440 cagttatata aatatattta tattttatag ttatataaat atatttatat tttatacagt 1500 tatataaata tatttatatt ttatacagtt atataaatat atttatattt tatacagtta 1560 tataaatata tttatatttt atacagttat ataaatatat ttatatttta tacagttata 1620 taaatatatt tatattttat acagttatat aaatatattt atattttata cagttatata 1680 aatatattta tatttatac agttatataa atatatttat attttataca gttatataaa 1740

SEL PCT 012.ST25

<210> 134

<211> 842

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(842)

<223> MAR of chromosome 2 genomic contig; 20483478..20484319

<400> 134

SEL PCT 012.ST25

<210> 135

<211> 645

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(645)

<223> MAR of chromosome 2 genomic contig; 20897566.,20898210

<400> 135

SEL PCT 012.ST25

tatgtatgta tatatacaca tatatattta tattatatat gtatattata tacatatatt
420
tatattatat atgtatatat atttatcata tttatatgta atatgcatgt gtaataaata
480
atatacacat ttatatatgt atattatata catatattta tattgtatat gtatatatat
540
ttatatatat ttgtatatca tatatttata tattgtatat ttatgtatat tatatattta
600
tatattatat atgtattata tadatatat gtaaatatat atat

<210> 136

<211> 722

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(722)

<223> MAR of chromosome 2 genomic contig; 21664541..21665262

<400> 136

SEL PCT 012 ST25

ca 722

<210> 137

<211> 305

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(305)

<223> MAR of chromosome 2 genomic contig; 22834991..22835295

<400> 137

<210> 138

<211> 352

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

352

<220>

<221> misc binding

<222> (1)..(352)

<223> MAR of chromosome 2 genomic contig; 25277762..25278113

<400> 138

tattatatat ttatatttat ttatatattc ataaatatat atatttatat ta

<210> 139

<211> 342

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(342)

<223> MAR of chromosome 2 genomic contig; 25378452...25378793

<400> 139

tatgtacata tatatttat atattatata taatatat tatatgatat atataatata 60

SEL PCT 012.ST25

<210> 140

<211> 663

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(663)

<223> MAR of chromosome 2 genomic contig; 30209437..30210099

<400> 140

SEL PCT 012.ST25

tatataatat agcatataca atatattata ttatatacaa tatataatat agcatataca 600 atatagtata ttatatacaa tatataatac agcatataca atatagtata ttacatacag 660 tat 663

<210> 141

<211> 1200

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1200)

<223> MAR of chromosome 2 genomic contig; 31725089..31726288

<400> 141

SEL PCT 012.ST25

<210> 142

<211> 325

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(325)

<223> MAR of chromosome 2 genomic contig; 32147252..32147576

<400> 142

SEL PCT 012.ST25

aatatataat atatttatat ataac

<210> 143

<211> 507

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(507)

<223> MAR of chromosome 2 genomic contig; 32312662..32313168

tatataaata ttatattat attattata taaatatta ttatataaat 300

attatatta tattattat ataaatatti attatata titatataaa tattatta 360

tatttatata aataatatat aaataaatat tttatatgta tataaatatt atttatatta 420

taatataaat attatattta tatttat

507

60

<210> 144

<211> 339

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<220>
<221> misc_binding
<222> (1)(339)
<223> MAR of chromosome 2 genomic contig; 3365111833651456
<400> 144 aaatataata tattattat atataatata aatgatatat tatgtatata taaaatataa 60
ataatatatt atgtatatat aaaatataaa tattatttat
ttatatataa aatataaata ttatattatt tatatataaa atataaataa tatattat
atatataaaa tataaataat atattattta tatataaata atatataaaa tataaatata 240
tattatatat aaataaaata tatatattat atatataaat ttatatataa tatataaaat 300
ataatatata tatttaatat ttattatata atatataat 339
<210> 145
<211> 461
<212> DNA
<213> Homo sapiens
<220>
<221> misc_binding
<222> (1)(461)
<223> MAR of chromosome 2 genomic contig; 4507305345073513
<400> 145 tgtgtataca tatatacgtg tacatataca tatatacatg tgtatatata tacgtgtaca 60

SEL PCT 012.ST25

tatacatata tacatgtgta tatatatgta catatacata tatacatgtg tatacataca

120
tatatacatg tacatataca tatatacatg tgtatacata catatataca tgtacatata

180
catatataca tgtgtatact tacatatata catgtacata tacatatata catgtgtata

240
tatacatata tacacgtaca tatacatata tacatgtaca tatatacatg tatacatata

360
tacatgtaca tatgtacata tatacatgt tacatatata catgtacata tgtacatata

420
tgtacatacg cacagataga catatataca tatgtacata c

461

<210> 146

<211> 1162

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1162)

<223> MAR of chromosome 2 genomic contig; 45487691..45488852

<400> 146

attatattat ctatataaat ctattatatc tattatatta totatataat atotattata 60 tatattatat tatotataa aatotattat atatattata tatotatat aaatotatta 120 tatatatat attatotata tatotattat atattatat atattatatt atattatatat 180 totattatat atattatatt atattatatt atattatatat 180 atotatataa tatotattat atattatatt atattatata 180 atotatataa tatotattat atattatata 180 atotatataa tatotattat atattatata 180 atotatataa tatotattat atattatata 180 atotattata tatatataa 180 atotattata 180 at

SEL PCT 012.ST25

atattatata taatatctat tatatctatt atatattata tatataatat ctattatatc 600 tattatatat tatatatata atatctatta tatctattat atctattata tatatatcta 660 ttatatctat tatatatatt atatacataa tatctattat atctattata tatattatat 720 780 tatatgtact atctattata tctattatat ctattatata tatactatct attatatcta 840 ttatatatat tatatatata ctatctatta tatctattat atatattata tatatactat 900 ctattatata totattatat atattatttt atattatata tagtatotat tagatatatt 960 atattatatt atatataata totattatat atattatatt atattataaa taatatatat 1020 ataattaata taatatotaa ta 1162

<210> 147

<211> 562

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(562)

<223> MAR of chromosome 2 genomic contig: 45516233..45516794

<400> 147

SEL PCT 012.ST25

120 atatacatat tatatatatt atatatacat attatatatt atatataata tatacatatt 180 240 ttatatataa atattatata tottatatat aaatataata tataatatat ataatatta 300 360 420 tatattatat aaatatatat aaatatataa aatatataaa tatgtaaaat ttatatttat 480 tacataatat atactatata ta 562

<210> 148

<211> 801

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(801)

<223> MAR of chromosome 2 genomic contig; 45727251..45728051

<400> 148

SEL PCT 012.ST25

360 420 480 540 600 660 720 780 atatatatat atatatagaa t 801

<210> 149

<211> 346

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(346)

<223> MAR of chromosome 2 genomic contig; 50937238..50937583

<400> 149

SEL PCT 012 ST25

taaaatatat attatattat ataaaatata tattatacta tatata 346

<210> 150

<211> 462

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(462)

<223> MAR of chromosome 2 genomic contig; 55672627..55673088

<400> 150

<210> 151

<211> 401

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<220>	
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<222> (1)(401)	
<223> MAR of chromosome 2 genomic contig; 56081352560	81752
<400> 151 tatacatgta tgtattcgta tatgtatgtt atatatgtat atgtgttata tacatataca	60
tatatacatg tatatgtgtt atatacatat acatatatac atgtatatgt gttatataca	120
tatacatata tacatgtata tgtgttatat acatatacat atatacatgt atatgtgtta	180
tatacatgtg tatgtgtata tgtatatata catatatgtg tatgtgcatg tgtatatata	240
catatatgta tatgtgtata tgtatatata catatatgta tatgtgtatg tgtatacgta	300
tatatacata tatgtgtatg tgtatgtgta tacgtatata tatacatata tgtgtatgtg	360
tatacgtaca tatacatata tgtgtatgtg tatacgtaca t 401	
<210> 152	
<211> 765	
<212> DNA	
<213> Homo sapiens	
<220>	
<221> misc_binding	
<222> (1)(765)	
<223> MAR of chromosome 2 genomic contig; 56404208564	04972

<400> 152

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aaagaatata tattatatat tatgtaaaga atatatat	120
tatattatat aatatataaa gaatatatat tatatattat ataaagaata tatattatat 1	180
ataatatata aagaatatat aatatataat atataaagaa tatatattat atataatata	240
taaagaatat atattatata taatatataa agaatatata ttatatatta tataaagaat	300
acatatatat aatatataaa gaatatatat tatatataat atataaagaa tatatattat	360
atataatata taaagaatat atattatata taatatataa agaatatata ttatatata	420
tatataaaga atatatatta tatataatat ataaagaata tatattatat atattatata	480
aagaatatta tatattatat aaagaatata tattatatat aatatataaa gaataaacat	540
atatactata tataaagaat atacattata tatactatat ataaagaata tacattatat	600
atactatata taaagaatat atataatata taaagaatat acattatata taatatataa	660
agaatatatt atatattata taaagaatac attataatat aaagaataca ttatatataa	720
tataaagaat acattataat atataaagaa tatatataat atata 765	

<210> 153

<211> 443

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(443)

<223> MAR of chromosome 2 genomic contig; 61953416..61953858

<400> 153

tttatatatt atagataaaa ttatattata ttacatgtaa tatataatat gtaaaatata 60 ttatataca tatataatat ataatatgta aaatatata tatacatat ataatatata 120

Seite 137

SEL PCT 012.ST25

atatgtaaaa tatattatat tacatatata atataaaata ttacatataa tatatttac

ataaatatat attatctatt acatattat tatatgtaat aatatgtaca tatgtataaa 240
tatgtatata tttatacata tgtatatatt atatatacat atatatgtat atattatata 300
tacatatata tgtatatatt atattatata tacatatata tgtatatat tatatatata 360
tacatatata tgtatatatt atattatata tacatatata tgtatatata ttataaatat 420
gtataataaa gatttatatg taa 443

<210> 154

<211> 372

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(372)

<223> MAR of chromosome 2 genomic contig; 62076211..62076582

<400> 154

<210> 155

SEL PCT 012.ST25

<211> 484

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(484)

<223> MAR of chromosome 2 genomic contig; 62158581..62159064

<400> 155

attatatata atataaaaat tatacatatt attttattat atattatata cataatatat 60

atataaaata tatataaat ataaaatata tattatatgt aattatatat aatataaaat 240

aatatatgaa ataagatata tactatatat aatatatata atttacatat aagatatata 480

tcat

<210> 156

<211> 644

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<221> misc binding

<222> (1)..(644)

<223> MAR of chromosome 2 genomic contig; 68145036..68145679

<400> 156

<210> 157

<211> 530

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(530)

<223> MAR of chromosome 2 genomic contig; 71257289..71257818 Seite 140

SEL PCT 012.ST25

<400> 157 atatctatta tatttatata ctttatataa attatatcta ttatatttat atactttata	6	30
taaattatat ctattatatt tatatacttt atataaatta tatctattat atttatatac	1	120
tttatataaa ttatatctat tatatttata tactttatat aaattatatc tattatattt	18	30
atatacttia tataaatata taattatatt tatatactti atataaatat aattataa	at	240
atattlatat actitatata aatataatta taaatatatt tatatactit atataaata	at	300
aattataaat atatttatat actttatata aatataatta taaatatatt tatatact	tt	360
ataattatat gitatattia taattatatt tatataattc ataattatat acattatgit	4	420
tatagttata taatttataa ttatatacat tatatttata ttiatataat ttataattat	4	180
ataaattata taaattatat aaattatctt taatttatat tatataatct	53	0

<210> 158

<211> 337

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(337)

<223> MAR of chromosome 2 genomic contig; 73413615..73413951

<400> 158
 acttatatta tataacta tattattgta tattaatata aattaatgat atataatata 60
 ttaattatat attattatat gtgatataaa atacttatat ttatactgta tatatgtata 120
 tacacacata tatgtatata tgtatatata cacatatgta tatatgtata tgtatatatg
 180

SEL PCT 012.ST25

tatactgtat atatgtatat acacacatat atgtatatat gtatatgtat atatgtatac 240
tgtatatatg tatatacata tatacatata tgatatatat cacatatatg tgatatataa 300
atatatttat ataaatataa tattaatatt tatatta 337

<210> 159

<211> 1340

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1340)

<223> MAR of chromosome 2 genomic contig; 77011049..77012388

<400> 159

atgtattta tatagtatat attatgtatt atattgatat aattatataa caattattta 120 180 ataattoata tatattata tattaaataa ttoatatata tttaaataat taatacatat 240 300 ttataoatta aattaatata tattatata ttaaattaaa tttaatatat tatatatta 360 tataatttaa atttaataat taattaatt taatttaatt taatataatt aaaatatatt 420 480 540 tatatttaat atataatata tatttaatat ataatatatt taatatataa tatatatta 600

SEL PCT 012.ST25

780 840 atatttaata tataatatat atttgatgta taatatattt aatatataat atatatttga 900 960 totataatat atttaatata taatatatat tigatgiata atatatitaa tatataatat 1020 tataatatat atttgatata taatatattt aatatataat atatatttga tatatattta 1080 tatatttaat atataatata tatttgatat ataatatatt taatatataa tatatattig 1200 atatataata tatttaatat ataatatata titgatatat aatatattta atatataata 1260 tatatttgat atataatata ttttcttatt aattatttat atataatata taaatatata 1320 ttaattaatt atatattaaa 1340

<210> 160

<211> 937

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(937)

<223> MAR of chromosome 2 genomic contig; 78226855..78227791

SEL PCT 012.ST25

tatatatoto tatatatoto tatatataca tatatotota tatatotota tatatacata 180 240 tototatata tototatata tacatatato totatatato totatatata catatatoto 300 tatatatgtg tatatataca tatatgtgta tatatgtgta tatatgtgta tatatacata tatgtgtata tatgtgtata tatacatata tgtgtatata tgtgtatata tacatatatg 360 420 totatatato totatatoto totatatata catatatoto tatatacaca catatatoto tatatatgtg tatatataca tatatgtata tatacatata tgtgtatata tgtgtatata 480 tacatatato totatatato totatatata catatatoto tatacataca tatatotota 540 600 tatatotota tatatacata tatototata catacatata tototata tototata tacatatato totatacata catatatoto totatatoto tatacataca tatatotog 660 tatatatgtg tatacatatg tgtgtatatg tgtatatata catatatgtg tgtatatatg 720 780 totatatata catatatoto totatatato totatatata catatatoto totatatato totatatata catatatoto totatatato totatatata catatatoto totatatato 840 tgtatatata catatatgtg tgtatatatg tgtatatata catatatgtg tgtatatatg 900 937 totatatata catatatoto totatatato totatat

<210> 161

<211> 1350

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1350)

<223> MAR of chromosome 2 genomic contig; 79287748..79289097

<400> 161

SEL PCT 012.ST25

tatatatatt atatatatag taactgttct attatatat tattatatat atttctgttc	60
tattatatat tatatatatt atattatata ttatatgtaa tatattatat atattataag	120
taatatatta tatatattat atgtaatata ttatatata	180
tattatatgc aatatgttat atatattata tgcaatatgt tatatatatt atatgcaata	240
tattatatat attatatgca atatattata tataatatat gtaatatatt atattatata	300
ttatatgtaa tatcttatat attatatgta atatattata tatattatat	360
atatatatta tatgtaatat attatatatt atatgtaata tattatctta tatatattat	420
atgtaatata ttatattata tattatatgt aatatatat	480
tatatgtaat atatattata tgtaatatat tacatattat atgtaatata tattatatgt	540
aatatattac atattatatg taatatatta catattatat gtaatatatt atatgtatta	600
tatgtaatat attatatgta ttatatgtaa tatattatat gtattatatg tattatatgt	660
aatatattat atgtattata tgtaatatat tatatattat atgtaattat attatatgta	720
atatattata ttatatatta tatatattat atgtaatata ttatattata tattatatat	780
attatatgta atatattata ttatatatta tatatattat atgtaatata ttatattata	840
tattatatat attatatgta atatattata ttatatatta tatatattat atgtaatata	900
ttatattata tattatatat attatatgta atatattata ttatatatta tatatattat 9	60
atgtaatata ttatattata tattatatat attatatgta atatattata ttatatatta	1020
tatatattat atgtaatata ttatattata tattatatat attatatgta atatattata 1	080
ttatatatta tatatattat atgtaatata ttatattata tattatatat attatatgta 1	140
atatattata ttatatatta tatatattat atgtaatata ttttatatta tatatattat 12	200
attatatatt atatgtaata tattatatta tttattatat attatatatt atatgtaata 12	260
attatatta tttattatat atattatatt atttatta	0
atattatatt atatatattt ctottctaat	

<210> 162

<211> 332

SEL PCT 012.ST25

<212> DNA

<213> Homo sapiens

<220>

<221> misc difference

<222> (1)..(332)

<223> MAR of chromosome 2 genomic contig; 81142998..81143329

<400> 162

ctatgtatat aactatatat aactattata taacttaata agatatataa ctattatata 60

acttaataag ttatatataa ctattatata taacttaata agttatatat aactattata 120

taacttaata agttatatat aactattata taacttatta agttatatat aactatatat 180

aacttaataa gttatatata actattatat aacttaataa gttatatata actattatat 240

aacttaataa gttatatata actattatat aacttaataa gttatatata actatatata 300

acttatatac aacttattaa gctatatata ta

332

<210> 163

<211> 327

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(327)

<223> MAR of chromosome 2 genomic contig; 84019536..84019862

SEL PCT 012.ST25

<400> 163 actgacagta tacatactgt atatatatac agtatgtata catatacagt atgtatacta 60
tatacagtat gtatactgta tatatatata cagtatgtat actgtatata tatacagtat 120
gtatacgtat gtatactgta tatatgtatt atagtgtata tatgtattat agtgtatata 180
tgtattatat atattatagt gtatgtatta tatgtgtata tacatataat atattataca 240
tatacatatg cacaatatgt atatgtatta tatgtattca tatacatata tgtatatgta 300
taatatatgt atacatataa tacacat 327

<210> 164

<211> 407

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(407)

<223> MAR of chromosome 2 genomic contig; 1448030..1448436

<400> 164

SEL PCT 012 ST25

<210> 165

<211> 1959

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1959)

<223> MAR of chromosome 2 genomic contig; 2117630..2119588

<400> 165

tatacatgtt atagtgtata tagtatacta atatataatg tatgtatgtg tatacatata cacatataat atacacatat ataatatata tagtatataa taatgtataa tatataatat 120 ataatataaa atgtatagta tactacatat ttatatatag tatatagtat gcatagtaca 180 tatatactat atatgtagta tactatagtg tatatatagt acaccatata tagtataaat 240 atactatata gtatatgtac tatatatata ctatatagta tatacagtat acatatatag 300 tatacctata ctatatagta tatatagtgt gcgtatacta tatagtatat atagtgtgcg 360 tatactatat agtatatata gtgtgcgtat actatatagt atatatagtg tgcgtatact 420 atatagtata tatagtgtgc gtatactata tagtatatat agtatacata tatagtgtgc 480 gtatactata tagtatatat agtatacata tatagtatgc gtatactata tatagtatac 540 atatagta tatctagagt atatgtagta tgtatagtat atatagtcta catactgtat 600 atacagtata tatatactot atagtatact atacagtata gtatactata tagtatacaa 660 tatatgtata ctatagaaac acactatata tagtatacta tatatactat atactatata 720 ctatatatag tatactatat atactacata ctatatatag tgtatgtata gtatatataa

PCT/EP2004/011974 WO 2005/040377

SEL PCT 012.ST25

tatatattat atgtatatta tagtatatta tactattata tattatatat tatattatat 900 attatataat ataatataat tatatattat aaaatatata tttttatatt atatattttt 960 atataaatat ataatatt atatattata tatagtataa tatataatat gttatatagt 1140 atcttatact attatactat atatattata tagtgtatat atagtatact atatatagtg 1200 tatatagtgt atactatagt gtatatagtg tatactatag tgtatatagt gtatactata 1260 tacactgtat atagtagtgt atactatata cactgtatat agtagtgtat actatataca 1320 ctgtatatag tagtgtatac tatatacact gtatatagta gtgtatacta tatacactgt 1380 atatagtagt gtatactata tacactgtat atagtagtgt atactatata cactgtatat 1440 agtagtgtat actatataca ctgtatatag tagtgtatac tatatacact gtatatagta 1500 gtgtatacta tatacactgt atatatagta tattatatat actatatatg tatatatagt 1560 atacatatat attatatata cagtatatat agtatatata ctatgtagta tatatagtat 1620 atatactata tagtatgtat agtatactat atagtatata tagtatatta tatagtatat 1680 atactatata otatatata tatattotat atataotata tatactatat aotatatata 1740 gtatattgta tatatagtat attgtatata tagtatacat agtatgtata tatagtatat 1800 atagtataca tatatagtat gtacacagta tatatagtct atatgtatac tacatatagt 1860 atacatgtat actatactac atatagtata catgtatact atactacata tagtatacat 1920 gtatagtata ctacatatac tatacatgta tagaatact

<210> 166

<211> 520

<212> DNA

<213> Homo sapiens

<220>

SEL PCT 012.ST25

- <221> misc_binding
- <222> (1)..(520)
- <223> MAR of chromosome 2 genomic contig; 2119984..2120503

<400> 166

tatgitatgoa togtatacat atatagtata tatatgtatg catogtatac atatatacag
tatatatagt atgcatogta tacatacagt atactatata tacagtatat acagtatat acagtatact
atatatacag tatatacagt atactatata tacagtatat acagtatact gtatatacag
tatatacagt atatatagta tactatata tacagtatata tacatgtat totatatata
gtatagtgta catagtatac atatagtata cactatacta tatatagtat actatatata
gtatatacag tatatatagt atactatata tagtatata tatatagtat actatatata
300
ctotatatag tatatatagt atactatata tagtatatat gtatactata tatagtgtat
420
gtatagtata gtgtatatat agtatatata catatatagt atatatatac actatatatt
420
gtatagtata gtgtatatat agtatagtat atgtatatat acacatgtat acatgtatat
480
atgtatacta atatatacta atatatgtat aaatatatat

- <210> 167
- <211> 954
- <212> DNA
- <213> Homo sapiens
- <220>
- <221> misc binding
- <222> (1)..(954)
- <223> MAR of chromosome 2 genomic contig; 2578285..2579238

<400> 167

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tattatatat aactttataa tatataatat atattatata taactttata atatataata 60 tatattatat ataactttat aatatataat atatattata tataacttta taatatataa 120 180 240 300 atataatata tattatatat aactttataa tatataatat atattatata taactttata 360 540 aatatataat atatattata tataacttta taatatataa totatattat atattatata ttatatatta tatataactt tataatatat aatotatatt atatattata tataacttta 600 taatatataa tatataatat aatatataac tttataatat atatatcata tattatatat 660 720 780 840 ttatatataa cittataata tatattatat ataaciitat aatatatatc atatattata 900 tataacttta taatatatat catatattat atataacttt ataatatata toat 954

<210> 168

<211> 452

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(452)

<223> MAR of chromosome 2 genomic contig: 3836217..3836668 Seite 151

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<400> 168	
tttatatata aatatatat ttatatatat ttatatataa tacatatata tcttatatat 60	
ataaaatata tatacatatt tatatataaa atacatatgt attatataca tttatatata 120)
atacatatgt attatataca attatataat acatatgtat tatatacaat tatataatac 18	0
atatttataa atatatatat ttatatttat atatatttat atataaataa atatatattt 240	
atagatttat ttatataaat atatatttat ataaatatat atttatatat atttatataa 300	
atatatattt atatatattt ctatatatat atataaatat atgtataaat atatatat	
atacatatat tcatataaat atatatattt atacatgtat ttatatgaat atatatttat 420	
acatgtaatt atatgaatat atatttatac at 452	
<210> 169	
<211> 417	
<212> DNA	
<213> Homo sapiens	
<220>	
<221> misc_binding	
<222> (1)(417)	
<223> MAR of chromosome 2 genomic contig; 38376663838082	
<400> 169	
gatatatata tttatataaa tatatatata aagagatata tttatatatt tatttatata 60	
aatatatttc tttatataaa gatatatgta aatatattta tttatataaa tatatttata 120	

PCT/EP2004/011974 WO 2005/040377

SEL PCT 012.ST25

300 tataaatata aatatata aatataaata tataaatgta taaatatata aatataaata 360 tatataaata totaaata tataaatata taaatatata aaaatatata taaatac 417

<210> 170

<211> 1197

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1197)

<223> MAR of chromosome 2 genomic contig; 6294846..6296042

<400> 170

tatatactaa tatutatata taaatatata aatatatata cacgtotata tataaatata tatotatata taaatatata tacatatato tatataaaaa tatatacota tatacotata 120 180 tacqtatata tagatatata cgtatatacg tatatacgta tatatagata tatacgtata 240 tacgtatata tagatatata cgtatatacg tatatacgta tacatgtgta tatacgtata 300 tacacatata cutatacatu tutatatacu tatatutata cattatatat acutatatat acatatatot atacatotat atataaatat atacatatat otatatata tacatatato 360 taatatatat attatatata atatattata tattatatat aatatataca tatataatat tatatataat atatotatat tatatataca tatotatata totacatatt atatatotat atatgtacct attatatata catatgtata tatgtaccta ttatatatac atatgtatat

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<210> 171

<211> 362

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(362)

<223> MAR of chromosome 2 genomic contig; 6506971..6507332

<400> 171

tatatatagt gtatactata tatacgctat atgcacacat aaactatata tacagtatat

aatatgcgta tactatatac acagtatata ctacatgtat actatatata gtatataaga

tatatactat gtatataata tatatactag gtatatatat ccatatatat actatatatac

atagtatata catatatatg tagtatata tgtatatgta catatatatg tagtatgtat

240

atatatacat atatacacac tatagtatat acatatatat actatatata ccctatatag

300

SEL PCT 012 ST25

agtatattat atacagtata ctatatatac tatatatacc ctatatagag catgtctatg 360

ct

362

<210> 172

<211> 2578

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(2578)

<223> MAR of chromosome 2 genomic contig; 6507395..6509972

<400> 172

SEL PCT 012.ST25

780 catatatagt atatatgcta tatatactat atagcatata ctatatacta tatatacagt 840 atatatagca tatatagcat atataatata tatacttttg atatacatac tatatacagt 900 atatatagta tatatactgt ataaatatac tatatatacc gtatatgcac actatatgct 960 atatatacta tatacactat atacagtata tatagtacac tatactatat aaagtatata 1020 tagtatacag tacactatac tatatacatt atatatagta tatattatac atagtatata 1080 gtatataaat agtatatata gtatatacag tatatatata gcatacttta tatagtatac 1140 acagtatata gatactatat atgctatata tagtatctat atactgtata ttatatatac 1200 taatatagta tatatgtata tatatactgt atatataata tatacatata tagtatatat 1260 actatacata cacactatac atatgtatat atactataca tactatatac tatatatcct 1320 atatatacta tatagtatat tatatacct atatatacta tatagtatat tatatacct 1380 atatatacta tatagtatat tatatatact atataccata tatactatat atactgtata 1440 gtatactata tatactatat agtatactgt atatactata tagtatactg tatatactat 1500 atagtatact gtatatacta tatagtatac tgtatatact atatagtata ctgtatatac 1560 tatatagtat actgtatata ctatatatac tatatagtat actgtatata ctatatagta 1620 tactatatat actatatacc atatatacta tgtatatact atatatagta tatactatgt 1680 atatgctata tatagtatat atagtatata tgctatatat agtatatata gtatatatgc 1740 tatatataca gtctatatat agtatatata ctatatagac tatatatata gcatatatac 1800 tatatatact atatataata tatatggtat atacatagta totatatgta gtatotatat 1860 atagtaccta tatatactat atataggtac tatatatagt atatatactt tatatagata 1920 ctatatatag tatatatact ttatatagta tatatagtat atgtagcata tatagtatat 1980 atagtatata tagtatatag tatgtatagt atatatagat tatattgtat atacagtata 2040 tatactgtat atactatata aatagtacat acagtatata cagtatatat gtactatata 2100 tagtatatac agtatataca gtatatatgt accatatata gtatatacag tatatacagt 2160 atatatgcac tatatgttat atacagtata tacagtatat atgtactata taaatagaat 2220

SEL PCT 012 ST25

atactctata tacagtatat atgtactata taaatatata cactatgtac agtatatatg
tactatataa atagtatata cactatatac agtatatatg tactatatag tgtatacagt
tactatataa atagtatata cactatatac agtatatatg tactatatag tgtatacagt
atatacagta tataggtact atataggta tatacagtat atatgcacta tatggtatata
acagtatata tgcactatat atggtatata cagtatatat gtactatata tggtatatac
agtatatatg tactatatat ggtatataca gtatatatgt actatatatg gtatatacag
tttatacagt atatatgcac tatatatggt atatacagta tacatgtact atatatgg
2578

<210> 173

<211> 598

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(598)

<223> MAR of chromosome 2 genomic contig; 7770400..7770997

<400> 173

gigtattigta tatacatata ogtatctacg tatatacata tatigtattigt atatacatat 60 atgitattigta tatacatata tigtatatacg tatatacata tatigtattigt atatacatat 120 atgitatac gitatatacat atatigtatata ogtatatacg atatacatat atatigtattig 180 tatatacata tatigtatata catatataca tatatatiga atatacatata tatigtatigt 240 atatacatat acatatatig tatatacata tatagtatig tatatacatat acatatatig tatatacatat acatatigt atatacatat tatigtatig tatatacata tatigtatig tatatacata tatigtatig tatatacata tatigtatig tatatacata tatigtatig tatatacata tatigtatig tatatacatat acatatatigc atatatagatat acatatatigc atatatagatat atatacatat 420 atacatatigt acatatatac atatatacat atatigtatat acatatatigt acatatatigt acatatataca atatatacat atatigtatat acatatatigt 480

SEL PCT 012 ST25

atatatacat atatacatat gtacatatat acatatatac atatgtacat atatacatat 540 atagatatat atacacatat atagatatac titatatatat atatacatat 4598

<210> 174

<211> 1048

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1048)

<223> MAR of chromosome 2 genomic contig: 8332422..8333469

<400> 174

SEL PCT 012.ST25

<210> 175

<211> 375

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(375)

<223> MAR of chromosome 2 genomic contig; 8909678..8910052

<400> 175

tatatacaca tatatacgta tgaatatata tacacatata cgtatgaata tatataccca

tatacgtatg aatatacaca tatatatacg tacgtatata tatacacata tatacgtacg

tatatatata cacatatata cgtacgtata tatatacaca tatatacgta cgaatatata

180

tacacatata tacgtacgaa tatatataca catatatacg tacgaatata tatacacata

240

tatacgtacg aatatatata cacatatata cgtacgaata tatatacaca tatatacgta

300

cgaatatata tacacatata tacgtacgaa tatatataca catatatacg tacgaatata

360

tatacacata tatac

375

<210> 176

SEL PCT 012.ST25

<211> 563

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(563)

<223> MAR of chromosome 2 genomic contig; 10572503..10573065

<400> 176

attitataata tatatgtata aatatatgta tatattitata titaaatata tgatatata 60
tittatattia aatatacgta tatatattia tattitaaata tacgtgtata tattitatatt 120
taaatatacg tgiatatatti tatattiaaa tatacgtgta tatattitaa tittaaatata 180
cgitgiatata titatattia aatatacgtg tatatattia tattitaaata tacgtgtata 180
tattitatatti taaatatacg tgiatatatti tatattitaaa tatacgtgta tattitatatt 300
taaatatacg tgiatatitta tattitaaata tatgtatgta titataaata tatattitaaa 360
gtatatatti tataaatgtat acatgtatat ataaatatat atattitaaa tatattita 420
tatatatatti tatatattita tataagtata tatatattia aatatatgta tatattitata 480
tattitatata agtatatata tittaaatata tgiatatati tataatatat attittaaata 540
tatatittata tattitaatata 480

<210> 177

<211> 595

<212> DNA

SEL PCT 012.ST25

<220>

<221> misc binding

<222> (1)..(595)

<223> MAR of chromosome 2 genomic contig; 11609694..11610288

<400> 177

tataaatact atatatagta tatataatat tatatatact atatataaat atatgtagta

taaataatat ataatataga tatataatat aatataatat gttataaata taaatatatt 120

tatataattt aatttataat atataatata taatatataa tttaatttta taatatataa 180

tatataattt aattttataa tatataatat ataatatota aattatatat aatttaatat 240

atctaaatta tataatttaa atataaatat aatataaata tatctaacat aatatacata 300

acataaatat atatagtata tatagtacat ataaatatat atagtacata tagtatatat 360

tatatattat taaatataat aataatttat tatatatact atatattatt atgtattata 540

<210> 178

<211> 662

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(662)

<223> MAR of chromosome 2 genomic contig; 12699804..12700465 Seite 161

SEL PCT 012.ST25

<400> 178 60 120 tatggtatat atatatggta tatatatatt tgctatatat atagcagatc tgctatatat 180 atatatttgc tatatatata gcagatctgc tatatatatt tgctatatat atgctatata tatgictacat atatgictata tatatgictat atatatgicta tatatatgict atatatatgic 300 tatatatatg ctacatatat gctatatata tgctacatat atgctatata tatgctatat 360 ata tatgcta tatatatgct atatatatat gctatatata tgctatatat atatgctata 420 tatatgctat atatatatgc tatatatatg ctatatatat gctatatata tagcatatat 480 atatagctat atatatgcta tatatatagc ttatatatat gctatatatg ctatatatat 540 gctatatata tagctatata tatgctatat atagctatat atatgctaca tatatgctat 600 ata tatgeca tatgtatget atatatatge tatatatata tgetatatat atgetatata 660 ta 662

<210> 179

<211> 649

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(649)

<223> MAR of chromosome 2 genomic contig; 12821904..12822552

<400> 179

SEL PCT 012 ST25

tatotaatat tatatatata aattatatat tatacatato taatattata tatatataa 60 ttatatatta tacatatgta atattatata tatataaatt atatattata catatgtaat 120 attatatata tataaattat atattataca tatgtaatat tatatatata taaattatat 180 240 300 aattatatat tatacatata taatatatat aaattatata ttatacatat ataatatata 360 taaattatat attatacata tataatatat ataaattata tattatacat atataatata 420 tataaattat atattataca tatataatat atataaatta tatattatac atatataata 480 tatataaatt atatattata catatataat atatataaat tatatattat acatatataa 540 600 649

<210> 180

<211> 3191

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(3191)

<223> MAR of chromosome 2 genomic contig; 15356889..15360079

<400> 180

120

tatataatat aatatata atatatatta cotattaata tataataaaa tatatataat 180

SEL PCT 012 ST25

atatattaca tattattata taatatatat tatataacat atataacata tactatatat tatataacat atataattot atatotatta tatatattat atatacttat acataatata taaataatta aatatatott ataaatataa caaatatata acatatataa catatataac atatatata a ttacataaaa tatataatac ataatatata ttatocaaca tattatataa tatataacat ataatgtata ttatattata tcatatataa tacataatat ataatatatg atataatata atatattata tatgatataa tataatatat tatatatgtt ataatataat 540 atatattata tataggatat attataacat attacatatg atataataaa ttttatctta 600 tatataggat atattataat atatcacata tagcatatat taaaatatat tacatatagt 660 atattatata tactatatot atatatacat atagtatatt atagtatatt atacagtata 720 tattatatat actatatata gragtataca gratatatta tatatactat aratagragi 780 atacagtata tattatacag tatatattat atacactata ttatatatta totataatat 840 atactatata tagtatatta totagtatat attaaacata atagatatat agtatatact atagataata gatattatat agtatatagt atatattata tataatatat ataatatata ttatatacat atatgatata tgatatatta tatataatat atataatata taatatatgt 1020 aacatacata aatataataa catatataat atatattata tattatatta tatatataa 1200 atactatata ttacacatta tacattattt ataatatata attaatatat aacatatat 1260 agataacata taattatatc totaacatat ataagatata attacatata taacatatat 1320 aattatatat atatttatot aattatatat gaaattatat atgacatata aaattatata 1380 ttatatatgt tatatgtatt atatattata tatgttatat atgttatata taacatatat 1440 aacatatata acacacacat ataacatata taacatatat tacatatata acatatataa 1500 cacatatata attatctaac atagataata tatataatat ataatataac atatatata 1560 tatattatac acticattat attatatata ttatacataa tatataatat atatgatata 1620 atataataca ttgtatatac gatataatat atattgtaca tagtataata tacatatata 1680

SEL PCT 012.ST25

gtatattatg tataacataa tatatagtat attatgtata acataatata tagtatatta 1740 tgtataacat aatatatagt atattatgta taacataata tatagtatat tatgtataac 1800 ataatatata gtatattatg tataacataa tatatagtat attatgtata acataatata 1860 tagtatatta totataacat aatatatagt atattatgta taacataata tatagtatat 1920 tatgtataa c ataatatata gtatattatg tataacataa tatatagtat attatgtata 1980 tataatatac atattatata gtatattatg tatatataat atacatatta tatagtatat 2040 tatgtatata taatatacat attatatagt atattatgta tatataatat acatattata 2100 tagtatatta tgtatatata atatacatat tatatagtat attatgtata tataatatac 2160 atattatata gtatattatg tatatataat atacatatta tatagtatat tatgtatata 2220 taatatacat attatatagt atattatgta tatataatat acatattata tagtatatta 2280 tgtatatata atatacatat tatatagtat attatgtata tataatatac atattatata 2340 gtatattatg tatatataat atacatotta totagtatat tatgtatata taatatacat 2400 gttatgtagt atattatgta tatataatat acatgttatg tagtatatta tgtatatata 2460 atatatata a ggtgtatata tattatgtat atataatata taaggtatat atattatgta 2520 tgtatatata atatgtatat tatatataat atatattatt tatatacatt atgtatctat 2640 ataatatata ttatgtatat attaggtatc tatataatat atattatgta tatatattat 2700 gtatctatat aatatatat ttatgtatat atattatgta tctatataat atatatatta 2760 tatgtatatt atgtatctat ataatatata taatgtatat agatatatta tatattatgt 2820 atatatatta tgtatctatt ttatatataa tgtatataga tatacaatat atattatgta 2880 cataatatat tacatattat gtatatatac ataatatata atatattatg tatatataca 3000 tgtatatata ttacatatat tatototata tatattatac ataatatata tactacatta 3180

SEL PCT 012.ST25 3191

tacataatat g

<210> 181

<211> 314

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(314)

<223> MAR of chromosome 2 genomic contig; 728676..728989

<400> 181

tgtgtatata tgtatatata atatatatta tataatatgc atatgtataa aatatgtata 6

ttatatatgt atattttata tatatgtata tattatatgt atattttata tatgtatatt 120

ttatatatat gtatatatta tatatgtata ttttatatat atgtatatat tatatgtata 180

ttttatatat atgtatatat tatatatgta tattttatat atatgtatat attatatatg 240

tatattttat atatatgtat attttatata tatgtatatc atatatatgt atatattata 300

tatatgtata tctt

314

<210> 182

<211> 423

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

SEL PCT 012.ST25

<222> (1)..(423)

<223> MAR of chromosome 2 genomic contig; 737493..737915

<400> 182

<210> 183

<211> 724

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(724)

<223> MAR of chromosome 2 genomic contig; 1069556..1070279

<400> 183

tattataata tattatatac attatattgt atatatacta tatatggtat atatagtata 60 cataatata aatutatatt qtaatataca ttatatata acatagtata attatataa 120

SEL PCT 012.ST25

180 tatataatgt atattataat gtattatata gtataatata atataatata cattatatag 240 tattocatta tatatoctat ataatatata atatattato tatatataca ttatatatac 300 360 tacaatatat aatgtatatt atatagtatg tataatgtaa tacattatac atagtacata 420 aagtatatta taatatatta taatatataa tatacattat atattataat gtatataata 480 tattgtatat atactatata taatgtatat acaattatat ataattgtat atatacatgt 540 atatgtatat gtatatatac atgtatatgt atgtgtatat atacatatat gtatatgtat 600 gtgtatatat gtatatgtat atatgtatat gtatacgtat atatgtatat acaatgtata 660 tataatgtat ataaaaatat ataatatata caatatgtat ataatgtata taattatata 720 atat 724

<210> 184

<211> 383

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(383)

<223> MAR of chromosome 2 genomic contig; 2719918..2720300

SEL PCT 012.ST25

ataaaaatat ataatatata aaa

383

<210> 185

<211> 309

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(309)

<223> MAR of chromosome 2 genomic contig; 4994249..4994557

<400> 185

tataatatat aattottata acattataac aattatatat tatatataat acaattatat 60 atatataata tatcatatat gitatatatt tiattatata atatatata tatataatat 180 atatatatta tatataatat atattatata ttaaatatta tatatataat atatataaca 300 ttattgtta

309

<210> 186

<211> 740

<212> DNA

SEL PCT 012.ST25

<220>

<221> misc_binding

<222> (1)..(740)

<223> MAR of chromosome 2 genomic contig; 5034916..5035655

<400> 186

<210> 187

<211> 847

<212> DNA

SEL PCT 012.ST25

60

180

660

<220>

<221> misc binding

<222> (1)..(847)

<223> MAR of chromosome 2 genomic contig: 6074678..6075524

<400> 187

aatatagaca taaatatata tgcataaata tatatatgca taaatatata taaaaatata 120

cataaatata tatgtataaa tatatataca cataaatata tgtatgaata tatatacata 240

aatatatatg tataaatata tatacataaa tatataaaga tatatacata aatatatata 300 360

420

aatatataaa tatatatata aatatata aatatataaa tatatatata aatatatata 480

540

tatataaata tatataaata tataaatata tatataaata tatataaata tataaatata 600 tatataaata tataaatata taaatatata tataaatata taaatatata taaatatata

taaatatata aatatata aatatatata aatatataaa tatatataaa tatatataaa 720

tatatataaa tatataaata tatataaata tatataaata tatataaata 780

tataaatata tatataaata taaatatata taaatatata aatatatata taaatatata 840

taaatat

847

<210> 188

<211> 784

<212> DNA

SEL PCT 012.ST25

<220>

<221> misc binding

<222> (1)..(784)

<223> MAR of chromosome 2 genomic contig; 6108986..6109769

<400> 188

60 120 180 240 300 360 tatatatatt atatatatat tttatatata taatatataa tatatatat atatatatat 420 tttatatgta taatatata tatatatat atatatat tatatata taatatgtaa 480 tatatatat atatatat tatatata atatatata tacataaaat atatattata 540 tataatatat ataatatata ttatatataa a atatatttt atgtataata tatattatat 600 ataatatata atgtatatti atatataaaa tatatatta tatacaatgt atatttatat ataaaatata tatttatata caatgtatat ttatataaat atgtgtttaa tatatgaaat 720 atatattat atataatata tatttaatot ataaaatata tattaaatat atatttatat 780

<210> 189

ttaa

<211> 381

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<	2	2	0	>

<221> misc_binding

<222> (1)..(381)

<223> MAR of chromosome 2 genomic contig; 10389032..10389412

<400> 189

tatacacata tagagtatat agagtatata tagagtatat ctatagagta tatatgtata 60

tagagtatat aatacagcct accatatata tagtatacat atatatatac totatatact 120

agtatatata cacagtatat atatgccata tatagtatct atatacttat atatagtatg 300

tatctatata cttatatata gtatgtatct atatactata tatagtatgt atctatatac 360

tatatagagt atatatgtat a

381

<210> 190

<211> 507

<212> DNA

<213> Homo sapiens

<220>

<221> misc_difference

<222> (1)..(507)

<223> MAR of chromosome 2 genomic contig; 11097807..11098313

<400> 190

SEL PCT 012 ST25

<210> 191

<211> 329

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(329)

<223> MAR of chromosome 2 genomic contig: 11234628..11234956

<400> 191

SEL PCT 012.ST25 329

tacagttaaa tatattaata tataatagt

<210> 192

<211> 584

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(584)

<223> MAR of chromosome 2 genomic contig; 797844..798427

<400> 192

<210> 193

<211> 363

<212> DNA

180

240

SEL PCT 012.ST25

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(363)

<223> MAR of chromosome 2 genomic contig; 1093824.,1094186

<400> 193

60

catatatata cacgtatata totatacaca tatatatota tatatataca catatataca 120

cacatatata cgtgtatata cgtatatacg tacatatata cgtgtatata cgtatatgcg

tacatatata cgtgtatata cgtatatgcg tacatatata cgtgtatata cgtatatgcg 300

tacatatata cgtgtatata cgtatatgcg tacatatata cgtgtatata cgtatatgcg tacatatata cgtgtatata cgtatatgcg tacatatata cgtgtatata cgtatatgcg 360

tac 363

<210> 194

<211> 545

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(545)

<223> MAR of chromosome 2 genomic contig; 3456187..3456731

SEL PCT 012.ST25

<400> 194 tattataata tatattiata tattataata tatattatat tatatatta tatattat	80
tatatattat attatatatt tatatattat aatatatat atattat	20
attataatat attatattat aatatatatt atattat	180
ttataatata tattatatta taatttatat attatatata ttataata	40
tatatatatt tatattataa tatatattat tatatattat	00
ttacaatata tattataaat atatatatta tattataaat atatattttt atattacaat	360
atatattata aatatatatt ttatattaca atatatat	420
caatatatat tataaatata tattatatta caatatatat	480
tatatgatat attatattta atatattata taacataata tataatata t aatatattaa	54
tataa 545	
<210> 195	
<211> 356	
<212> DNA	
<213> Homo sapiens	
<220>	
<221> misc_binding	
<222> (1)(356)	
<223> MAR of chromosome 2 genomic contig; 50015675001	922
<400> 195	-00

SEL PCT 012.ST25

<210> 196

<211> 321

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(321)

<223> MAR of chromosome 2 genomic contig: 5457330..5457650

<400> 196

<210> 197

<211> 361

<212> DNA

SEL PCT 012.ST25

<220>
<221> misc_binding
<222> (1)(361)
<223> MAR of chromosome 2 genomic contig; 81244698124829
<400> 197 tatatataat atatattata tatattatat aaattatata taatatgtaa tataaatttt 60
gtaatataaa ttatatata aaattatata taatatatat taatatatat aatataaatt 120
aatatatata atatataatt atatataatt tatatgatat atataaatat atattatata 180
taaattatat atatcataaa ttatatatca tataaattat atataatata cattatgtac 240
ataatatatg atatataata tataatatat attatatata
ataatatatg atatataata tataatatat attatatata
taatatata aaattataat atataatata tataaattat aatatataat atatataaat 360
taatatata aaattataat atataatata tataaattat aatatataat atataata
taatatata aaattataa atataatata tataaattat aatatataa atatataaa 360 t 361 <210> 198
taatatata aaattataa atataatata tataaattat aatatataa atataata
taatatata aaattataa atataatata tataaattat aatatataa atatataa aatatataa aatatataa aatatataa aatatataa aatatataa aatatataa aatatataa aatatataa aatatataaa aatatataaaa aatatataaa aatatataaaa aatatataaaa aatatataaaa aatatataaaa aatatataaaa aat
taatatata aaattataa atataatata tataaattat aatatataa atatataa aatatataa aatatataa aatatataa aatatataa aatatataa aatatataa aatatataa aatatataa aatatataaa aatatataaaa aatatataaa aatatataaaa aatatataaaa aatatataaaa aatatataaaa aatatataaaa aat
taatatata aaattataa atataatata tataaattat aatatataa atatataaa 360 t 361 <210> 198 <211> 418 <212> DNA <213> Homo sapiens
taatatata aaattataa atataatata tataaattat aatatataa atatataaa 360 t 361 <210> 198 <211> 418 <212> DNA <213> Homo sapiens
taatatatat aaattataat atataatata tataaattat aatatataa 360 t 361 <210> 198 <211> 418 <212> DNA <213> Homo sapiens <220> <221> misc_binding

<400> 198 atgtaactat atatatagta tatatagtat atatatacta tatagtgtgt atatatagta 60

SEL PCT 012.ST25

tatatatact atatagtgtg tatatatagt atatatatag tgtatatatc gtatatacac 120 tatatactat atagtgtata tatagtatat gtagtatata tagtatatat agtatagtat 180 atatagtata tatagtgtat atatactgta tatatagtgt acatagtata ctatatagta 240 tacatatagt acactgtata gtatatatag tatagtatat atagtataca tagtatacta 300 tatatagtat agtatacata gtatactata tagtatatag agtatatata cagtatacta 360 tatagtatat agagtatata tacagtatac tatatagtgt gtatagagta tatataca 418

<210> 199

<211> 394

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(394)

<223> MAR of chromosome 2 genomic contig; 13591477..13591870

<400> 199

<210> 200

SEL PCT 012.ST25

<211> 1194

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1194)

<223> MAR of chromosome 2 genomic contig; 14996824..14998017

<400> 200

taatatttat atatacatat aaaatttata tataatatat aatatttata tatacatata 60 aaatttatat atatataa tatttatata tacatataaa atttatatat aatatataat atttatatat acatataaaa tttatatata atatataata tttatatata catataaaat 180 ttatatataa taaatattta tatatacata taaaatttat atataattta tatataacat 240 ataatatta tatataaaat ttatatataa catatatta tatataattt atataaaca 300 tataatattt atataata tatatttatt tatacaattt atataata tataatactt atatatacat acataattta tatgatatat attatatata taatttatat gatatataat 420 atatctaata tatattatat atattatata tattatatat aatttatata atatatatta 480 540 tatataattt atataatata tattatatat ataatttata taatatatat tatatatata 600 atttatataa tatatattat atataattta tatataacat attttatata catatataat 660 ttatatataa tatatttta catatacata tataattttt atataatata aaatatttct 720 atatacatat ataatttta tataatataa aatatttcta tatacatata taatttttat 780 ataatatata tttctatata catgtctaat ttttatataa tatatatttc tatatacata 840

SEL PCT 012.ST25

acatatacat atataatttt tatataatat atatttatat atacatatat aattttataa 960
taatatatat tatatataca tatataattt atatacaaca tataatatat acatatataa 1020
ttaataca acatataata tttatgtata catatataat gtatacacaa tatataatat 1080
*
ttatatatac atatataatt tatatgtaat atatacatat ataatttata tgtaatatat 1140
atacatgtat aatttatatg tagtatatat acatotataa tttatatgta gtat 1194

<210> 201

<211> 487

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(487)

<223> MAR of chromosome 2 genomic contig; 14998429..14998915

<400> 201

tagtatacat ttacacatac atgtataatt atatgtaata tataatattt acatatataa 60 ttatagataa tatatatta catatacata tataattata tataatatat aatotttaca 120 tatacataca taattatata taatatatat ttaaatatac atatacaatt atatataata 180 tatatttaca tatgcatata taattataga taatatatat ttacatatac atatataatt 240 300 tacatataca attatatata atatatatti acatatgcat atataattat agataatata 360 tatttacata tacatatata attatatata atatataata tttacatata catatataat 420 480 tatatta 487

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60

360

<210> 202

<211> 421

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(421)

<223> MAR of chromosome 2 genomic contig; 16562490..16562910

<400> 202

aatatatota tatatatoaa tatatatota tatatoaata tatotatata tatoaatata 120 180 tatatatgta tatatgtata tatatgaata tatatgtata tatgaatata tatgaatata 240

tatatgaata tatatgaa tatatacgta tatatgaata tatacatgta totatatatg

tatgtatata tatgaatata tatgaatata tgtgtatata tatgaatata tatgtatata 300

tgtatatgaa tatatatatg aatatatatg tgtatatgaa tatatatgaa tatatatgtg 420

t 421

<210> 203

<211> 479

<212> DNA

<213> Homo sapiens

<220>

SEL PCT 012.ST25

<221> misc binding

<222> (1)..(479)

<223> MAR of chromosome 2 genomic contig; 21592301..21592779

<400> 203

<210> 204

<211> 870

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(870)

<223> MAR of chromosome 2 genomic contig; 22557584..22558453

<400> 204

tataatatat aatatacata atatgtatat tttatacaca atataaataa tatacataac

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atattttata tataatatat atattotata taataatata taatatata tattatatat aatatatata atatatata aaatatatat tatatataat atgtataata tataatattt 240 tatatataat atgtataata tatattttat atataataat atgtacaata tatattttat 300 atataataat atotacaata tatatttat atataataat atotacaata tatatttat 540 600 780 tatatataat atataatata taatatataa 870

<210> 205

<211> 1086

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(1086)

<223> MAR of chromosome 2 genomic contig; 30591960..30593045

<400> 205

SEL PCT 012 ST25

gtatatataa tatatattat attatgttat atattatgta gactatgtat taaatatatg 60 tatatattat atataaatat ataatatata titataatti ataattataa atatattat 120 aatatattit totaaatatt tatatattat atattatato taatgatata taataaatat 180 atatattata tattatatat titatatata ctatatatta tatagtatat attitatata 300 tactatatat tatatattat atattttata tatactatat attatatat atatattita 360 420 tttatatata ctatatacta tttattatat attttatata tactatatat tatatattat 480 atattttata tataatatat atttattata tattttatat attatatata tratatata 540 tatatttata tattatataa tatatattat atatagaata tataatatat attatataa 600 atatattatc atatgtaata atagatataa tatgtaatat ataaattata attatatatt 780 ttaatatatt aaatattatg tattaaatat atataatata tttataaata ttttatatat 900 aatatataca tatattaaca tatatgtata tatgtatata ttatatataa cattatatat 960 attatgttac atatactata ttttatatgt tacatatact atatattata tgttacatat 1020 aatatatata acatatatta taatatgtaa catattatat ataacatata atatatagta 1080 tatata 1086

<210> 206

<211> 406

<212> DNA

SEL PCT 012.ST25

<221> misc binding

<222> (1)..(406)

<223> MAR of chromosome 2 genomic contig; 36233909..36234314

<400> 206

<210> 207

<211> 797

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(797)

<223> MAR of chromosome 2 genomic contig; 36271745..36272541

<400> 207

SEL PCT 012.ST25

acacataaac atattacata catatacaaa ttatacacat atacatatat acatatatgt 180 atatacatac attatatata aatatatgta tataaaatgt acattatata tacatatata ttatotataa ataatatata aaataaacat aatatatatt tatagatatg atatatataa 300 360 tatatatgta tacatatata catatatgta tatataatgt acattataca tacataaaca 420 480 tactatatat actgtatata atatataata taatatatac tatatatact aaatataata 540 tacataatat aatatatact atatataata tataatatat aatatagtat atatactata 600 tataataatt acatattata tattatacat tatatattat ataattatta tatataatta 660 tatattacat actitigitata taatigtaaat atacattaga atatataatig tatatatatig 720 tacatatata atgtatatat gtatacatta tataaaactat atataaacat tatattatat 780 aaacattata tataaac 797

<210> 208

<211> 423

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(423)

<223> MAR of chromosome 2 genomic contig; 36498521..36498943

<400> 208

tattatatta tatatttaat attatatatt taatatatta tatatttaat attatatatt 60

taatatatta tatattaat attatatatt taatatatta tatattaat attatatata 120

SEL PCT 012.ST25

taa

423

<210> 209

<211> 304

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(304)

<223> MAR of chromosome 2 genomic contig; 37179891..37180194

<400> 209

gtgtatatat atcatatata ttatatcata tatatgtgta tatatatcat atattatatc 60 atatatatgt gtatatatat catatatata tcatatatgt gtatatatca tatatattat 120 atatcatata tgtgtatata tatcatatat tatatatcat atatatgtgt atatatcata 180 tatattatat atatcicata tgtgtatata tatcatatat aatatatatg tgtatatat 240 atatatcata tataacatat atatatgtgt atatacatat atatacatat tataacatat atatacatat atatacatat atatacatat atatacatat atatacatat atatacatatat 330

tgta

304

<210> 210

<211> 693

SEL PCT 012.ST25

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(693)

<223> MAR of chromosome 2 genomic contig; 38440448, 38441140

<400> 210

tatatattet tttatatatt atatataata tatattettt tatatattat atatagtata 60

tattettta tatattatat atagtatata ttettttata tattatatat agtatatatt 120

cttttatata ttatatatag tatatattct tttatatatt atatatagta tatattcttt 180

tatatattat atatagtata tattotttia tatattatat atataatata tattotttia 240 tatatoatat ataatatat titottitata tattatatat aatatatatt ottitatata 300

ttatatatca totatatata atatacaaaa tatatataga ttttatatat agattattac 360

ataatagaat atattatata ttatatataa tatatacata atatataata ttatatatga 420

tataatatat atcatatata tcatataata tatattatat atcatatatt atatataata 480

acaaaatcta tatataatat atattatatt atatataata tacataacta tataaaaaat 660

ataatatata atatataa tatataatat ata 693

<210> 211

<211> 471

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<220>

<221> misc binding

<222> (1)..(471)

<223> MAR of chromosome 2 genomic contig; 38887582..38888052

<400> 211

<210> 212

<211> 1221

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(1221)

<223> MAR of chromosome 2 genomic contig; 43885944, 43887164

SEL PCT 012.ST25

<400> 212 catataaaca tatattatat gtaacatata aacatattat atgtaacata taatatataa 60		
tatataaaca tatattttat atattatatg ttacatataa tatataatat ataaacatat 120		
attatatatt atatgtaaca tataatatat aatatataaa catatatttt atatataata 180		
tataaacata ttttatatat aatatataaa catattttat atataatata taaacatata 240		
ttttatatat aatatataaa catattttat atataatata taaacatata ttttatataa 300		
tatataaaca tataatatat ataatatata aaagtatata atataaatat atataatata 360		
aacatatata atataaatat atataaaata taaacatatg taatatataa acatatatta 420		
tatataatat ataaacatat attatacgta caatatataa acatatattg tacgtacaat 480		
atataaacat atattatacg tacaatatat aaacatatat tatacgtaca atatataaac 540		
atatattata cgtacaatat ataaacatat attatacgta caatatataa acatatatta 600		
tacgtacaat atataaacat atattatacg tacaatatat aaacatatat tatacgtaca 660		
atatataaac atatattata cgtacaatat ataaacatat attatacgta caataaacat 720		
atattatacg tacaatatat aaacatatat tatacgtaca atatataaac atatattata 780		
cgtacaatat ataaacatat attgtacgta caatatataa acatatatta tatgtataat 840		
atataaacat ataatatata atatatatta tatatatgtt tattatatat gtttatatat 900		
tatatataac atatattatt atattatata tgtttatata ttatatatta tataatatat 960		
atgtttatat attatatatt atataatata tatgtttata tattatatat tatataatat 1020		
atatgtttat atattatata ttatataata tatatgttta tatattatat attatataat 1080		
atatatgttt atatattata tattatataa tatatatgtt tatatattat atattatata 1140		
atatatatgt ttatatatta tatattatat aatatatat		
taaacttaca tattttatta a 1221		

<210> 213

<211> 543

<212> DNA

SEL PCT 012.ST25

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(543)

<223> MAR of chromosome 2 genomic contig; 45818200..45818742

<400> 213

tatgtatata tacatatata tttatacatg tatatatgta tatatacata tatatttata 60

catgtatata tatacatata tatttataca tgtatatata tacatatata tttatacatg 120

tatatatata catatatat tatacatgta tgtatatata catatatat tatacatgta 180

tgtatatata catatatatt tatacatgta tgtatatata catatatatt tatacatgta 240

tgtatatata catatatatt tatacatgta tgtatatata catatatatt tatacatgta 300

tgtatatata catatatatt tatacatgta tgtatatata catatatatt tatacatgta 360

tgtatatata catatatat tatacatgta tgtatatata catatatat tatacatgta 420

tgtatatata catgtatatt tatacatgta tgtatatata catgtatatt tatacatgta 480

tgtatatata catgtatatt tatacatgta tgtatatata catgtatatt tatacatgta 540

tac 543

<210> 214

<211> 463

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(463)

<223> MAR of chromosome 2 genomic contig; 47055478..47055940

<400> 214

tacacacata tatacatat atacacatat atacacatat atacacatat tatacacata tatacacata tatacacata tatacacata tatacacata tatacacata tatacacata tatacacata tatacacata tatacaca tatacacata tatacaca catatacaca catatacaca catatacaca catatacaca catatacaca tatacacata tatac

<210> 215

<211> 2482

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(2482)

<223> MAR of chromosome 2 genomic contig; 47492696..47495177

<400> 215

aatatatata aaatatatta tattotatgt aatatataga atatataaaa tatattotat 60 atattatata gaatatatat tttataatat atattattta tatattitta tatattita 120

SEL PCT 012.ST25

ttatttatat atttatatat aatttatata atttatacat ataatttata tataatttat 180 ataaattata tatataattt atatataatt tatatataat ttatataaat tatatatata 240 atttatatat aatttatatu atttttatat ataatttata tataatttat ataattttta 300 360 aatttatata taatttatat aatttatata tataatttat atataattta tataatttat 420 atatataatt tatataaat ttatataatt tatatatata atttatatat aatttatata 480 atttatatat ataatttata cataatttat ataatttata tatataattt atataattta 540 tatatataat ttatatatat aatttatata atttatatat atgatttata taatttatat ഒവ 660 tttataattt atatatttat ataatttata tatttataat ttatatattt atataattta tatatttata atttatatat ttatataatt tatatataat tattcatata tttatataat 780 aattattac atattatat atttatatat aatttatata tatttatata taatttataa 900 tatattttac attatattta atattatatg tataatttta tatcatatat aatatatatg 1020 atatatata ttttatatca tatataatat atatggtata tataatttta tatcatatat 1080 aatatatato otatatataa tittatatoa tatataatat atoatatata attitatato 1140 atataatata tattatatat aattttatat ctacatatta tatattatat atacaatttt 1200 atatctatct ataatatata ttatatatac aattttatat ctatataata tatattatat 1260 atacttttat attatatata aaatgtatat tatatatact tttatattat atataaaatg 1320 tttattttat atataaaatg tatattatat ataattttat tttatataaa aaatgtatat 1500 atatgtatat tatatataat tttatattat atataatatg tatattatat ataattttat 1620

SEL PCT 012.ST25

attatatata atatgtatat tatatataat tttgtattat atataatatg tatattatat 1680 ataattttat attatata atatgtatat tatatataat tttatattat atataatatg 1740 atattatata taatgtatat tatataatat atattatata ttataatata taatatacat 2220 tatatattac atattatata taatatatta tatattatat attacatatt atatataata 2280 tattatatat tatattaaat atatatttia tatattatat attatatat atataaaata 2340 aattatatat attatatata aa 2482

<210> 216

<211> 539

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(539)

<223> MAR of chromosome 2 genomic contig; 47561069..47561607

SEL PCT 012.ST25

<400> 216 aacagtaata tatcactaat atataataat atataacagt aatatatcat taatatat	aa 60
tatatcatta gtatataata ttaatatata ttaatatata atatatcata tacaatatta	120
atatatatta atatataata atatattatt aatgtataat agtaatataa tatattatca	180
atatatatta ctaatatata ataatatatc gttaatatat aatagatcat taatatataa	240
tgttaatata ttatgaatag ataatatatc agtatataat attaatatat taatatatta	300
tatattattt aataatatat aatatattaa taaataat	360
ttaatatatg actgtattat attattaata tataacaata tattatatat tatataataa	420
ttlattatat aatatataat aatatattat atattatata acatattaat aatacataat	480
aacattaata atatataata atgttaatat attattatat tatatattaa tatataata	539

<210> 217

<211> 336

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(336)

<223> MAR of chromosome 2 genomic contig; 52853648..52853983

<400> 217

SEL PCT 012 ST25

tatgttatat atattacatg tatattatat ataatataca tataaatttt aaatttagtg 300

tatattacat gtatattata tataatatat gtatat

336

<210> 218

<211> 406

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(406)

<223> MAR of chromosome 2 genomic contig; 54866263..54866668

<400> 218

<210> 219

<211> 1452

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

<220>

<221> misc binding

<222> (1)..(1452)

<223> MAR of chromosome 2 genomic contig; 55113305.,55114756

<400> 219

ataatatata atatatatto tatatlatat tattatatat tatatatlat taaatatata 60 180 tattatacta tatattatat aatatatatt atatataata atatagaata tataattata 240 tattatataa tatotoaata atotaatata taattatatt atttacatat tatataatat 300 atattatata taatataatt atatataatt aattataaat taattatata taattatata atataatata taatatacat aatatataat atataataca taatatacat aatataatat 480 attatatata atatataato ttatataatt atattatatt atataattaa ttatatotaa 600 ttaatataat ataattatta tatataatti titatataat ataatatata attatataat 780 taatataata tgattatata atatattatg tatattatat attatatat gtattatgta 840 tattatatat tatatattat gtatattata tattatgtat attatatat atgtatatta ttatatatta totatattat atataaatta tattatatat tatotatatt atatataata 1020 taaagtatat attatgtata ttatatataa tataaagtat atattatgta tattatatat 1080 aatataaagt atatattatg tatattatat ataatataaa gtatatatta tgtatattat 1140

SEL PCT 012.ST25

<210> 220

<211> 502

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(502)

<223> MAR of chromosome 2 genomic contig; 56350637..56351138

<400> 220

atatatetat ataacatata ta

<210> 221

<211> 794

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(794)

<223> MAR of chromosome 2 genomic contig; 57051633..57052426

<400> 221

aactatatat actatattat atagttatac tatatatact atatatataa gttatataac 60 tattatataa ctgtattat atagttata tatagttata actatatat aactgtatta tatagttata 120 taactattat ataactgtat tatatagtta 180 gttatatat ataactgtat tatatagtta tatatagtta 180 gttatatat atataactat attatataac tgtattatat agttatatat tatataacta 240 tattatata actgtattat atgttatata tatataacta 180 atatgttatat attatataac tgtattatat agttatatat actgtattat 180 atatgttatat attatataac tgtattatat agttataaa ctatattata actgtattat 180 atatagttat aaaactacta tataactgta ttatataatt ataaaattat actatataac 180 atatagttat aaaactacta 180 atatagttat aaaactatata 180 atatagttat atatagttat aaaactatat 180 aactatactg 180 atatagttataaactgt attatatagtt ataaactgtat tatatagttat atagttatata 180 agttataaaa ttatatata taactgtat tatatagttat aactatata 180 agttataaaa ttatatata taactgtat atatagttat ataactatat tatataactg 180 agttataaaa ttatatata taactgtat atatagttat atagttatat aactatata 180 agttataaaa tatatataa taactgtat atatagttat atagttatat aactatata 180 agttataaat gttatataact atatatataa agtgtattat atagttatat aactatataa 180 atataactgta tatataactgt attatataactgtat atatagttatat aactatataactgta 180 atataactgta tatataactgt attatataactgtat atataactgtat atatagttatat aactatataactgta 180 atataactgta attatataactgtatatataactgtattaactgtattaactgtattataactgtattataactgtattataactgtattataactgtattaactgtattaactgtattaactgtattaactgtattataactgtattaactgtattaactgtattaactgtattaactgtattaactgtattaac

ctatattata taac

<210> 222

<211> 300

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(300)

<223> MAR of chromosome 2 genomic contig; 57069272..57069571

<400> 222

acacatacat atatgtatat atgcacacac atatatatgt atatatacac atacatatat 60
gtatatatac atatatgtat atacgcacat acatatatgt atatatacac gtacatatat 120
gtctctatat atacacatac acatatgtat atacatatat gtgtatatat acacaatcat 180
atatgtatat acatatatac acatatacac aaacatatat gtatatacat atatgtatat 240
acatatatac acatatacac aaacatatat gtatatacat atatgtatat acatacacaa 300

<210> 223

<211> 370

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(370)

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<223> MAR of chromosome 2 genomic contig; 57235143..57235512

<210> 224

<211> 306

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(306)

<223> MAR of chromosome 2 genomic contig; 57693125..57693430

<400> 224

tacagtatata cacgtataaa tataaatata tacatgtata tacgtatata catgtataa a 120
tataaatata tatatgtata tacgtatata catgtataaa tatatatat tatatatgta 120
tatacatgta taaatatata tatatgtata tacgtatata catgtataaa tatatataca 180
tgtatatacg tatgttgtgt atacatacaa atctgtacat atatacatat atgttgtgtg 240

SEL PCT 012 ST25

tatatataca totatacatg tgtatgogta tatatgtata tgtatatata gtatatataa 300

tacatg

306

<210> 225

<211> 500

<212> DNA

<213> Homo sapiens

<220>

<221> misc_binding

<222> (1)..(500)

<223> MAR of chromosome 2 genomic contig; 59810331..59810830

<400> 225

tataatatta tatattatat

500

<210> 226

<211> 565

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(565)

<223> MAR of chromosome 2 genomic contig; 59974589..59975153

<400> 226

atatatgtat aatatgtata tatgtatata ttatgtatat gttatatatg taatatatgt 60 atgtatatat tatatatcat atataatata taatgtatat atatatatat 120

acatgtatat actatgtata tattgtatat attatatatg tatatataca tatacatata 180

taatatatac atatattata tacaatatat acatgtatat tatatacgat atatacatat 240

atattatata caatatatac atagtatata aatgtataca tacatacata tatacatatt 300

catacgtaca tatacgtata tgtatatgca tatatgtata tatgtgcata catatatatg 420

tatatacata tatgtacata tgtacatata cgtatatatg tacatatgta catatacgta 480

tatatgtaca tatgtacata tacgtatata tgtacatatg tacatatacg tatatatgta 540

catatgtaca tatatacata tatat

<210> 227

<211> 427

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(427)

<223> MAR of chromosome 2 genomic contig; 60605573..60605999

<400> 227 tatataatgt atataatgga tatagatata gatatagata tatattttat ataatatata atatatattt tacataatat ataatatata atacgtatta tatataatat ataatacgta 300 ttttatataa tatataatac gtattatata taatacgtat tatatattat ataatatata 360 atacgtatta tataatatac gtaattatat tttattataa tacgtattat atattatata 420 atatata 427

<210> 228

<211> 1199

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1199)

<223> MAR of chromosome 2 genomic contig; 61229949..61231147

<400> 228 gtatacatat ataaagtgta tatataatgt atatacatat atacatata aaagtatata

tataatatat acatatataa agtatatata taatatatac atatataaag tatatataat 120

SEL PCT 012.ST25

atatacatat ataaagtata tataatatat acatatataa agtatatata tcatatatac 180 atatataaag tatatatata atatacat atatacatat ataaagtata tataacatat 240 atacatatat aaagtatata taacatatat acatatataa agtatatata taatatatac 300 atatacat atataaagta tatataacat atatacatat atacagtata tataacatat 360 atacatatat acagtatata taacatatat acatatatac agtatatata acatatatac 420 atatatacag tatatataac atatacat atatacatga agtatatata acatatatac 480 atatatacat gaagtatata taacatatat acatatatac atgaagtata tataacatat 540 atacatatat acatgaagta tatataacat atacatat atacatatat aaagtatata 600 taacatatac atatatacat atataaagta taacatatac atatatacat atataaagta 660 tatataatat ataacatata catatataaa gtatatataa tatataacat atacatatat 720 780 catatataaa gtatatataa tatatatata catatataaa gtatatataa tatatataca 840 tatatacata tataaagtat atataatata tatacatata taaagtatat ataatatata 900 tacatatata catatataaa gtatatataa tatataca tatatacata tataaagtat 960 atataatata tatacatata tacatatata aagtatatat aatatatata catatataca 1020 tatataaagt atatataata tatacata tatacatata taaagtatat ataatatata tacatatata catatataaa otatatataa tatotataca tatatacata tataaaotat 1140 atataatatg tatacatata tacatatata aagtatatat ataatatgta tacatatat 1199

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<221> misc binding

SEL PCT 012.ST25

<222> (1)..(454)

<223> MAR of chromosome 2 genomic contig; 62181058..62181511

<400> 229

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<223> MAR of chromosome 2 genomic contig; 62190919..62191576

<400> 230

actatatata taactatata taactata tataactata tataactata tatataacta 120

SEL PCT 012.ST25

180 240 300 360 atatataact atatatatat aactatatat aactatatat atataactat atatataact 420 480 540 atataactat atatatata ctatatatat aactatat ataactatat atataactat 600 658

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SEL PCT 012.ST25

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attatattaa taatataa tatactaata tattaagaat atataatata	660
aagaatatat aatatactaa tattatatta ataatatat tttatattaa taatatatta	720
attattatta attaattatt aataattata taatattgat tatattaata ttatcaattt 780	0
aataatattg attatatatt atatattata tattatatat tatatattat	0
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tataatatat taataatata tattagatat aatataatat attaataata tatattagat	960
ataatataat atattaataa tatatattag atataatata atatattaat aatatatat	1020
agatgtaata taatatatta ataatatata ttagatgtaa tataatatat taataatata	1080
tattagatgt aatataatat attaataata tatattagat gtaatataat atattaataa	1140
tatatattag atgtaatata atatattaat aatatatat	1200
ataatatata ttagatgtaa tataatatat taatatatat	1260
aataatatat attagatata atataatata ttaataatat attagatata atataatata	1320
ttaataatat ataagatata atataatata ttaataatat ataagatata atataatata	1380
ttaataatat ataagatata atataatata ttaataatat atattagata tataatatat	1440
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<211> 333

<212> DNA

<213> Homo sapiens

SEL PCT 012.ST25

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<221> misc binding

<222> (1)..(480)

<223> MAR of chromosome 2 genomic contig; 63240325..63240804

<400> 233 60

SEL PCT 012.ST25

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<211> 302

<212> DNA

<213> Homo sapiens

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<222> (1)..(302)

<223> MAR of chromosome 2 genomic contig; 63935480..63935781

<400> 234

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<222> (1)..(407)

<223> MAR of chromosome 2 genomic contig; 63935888..63936294

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<212> DNA

<213> Homo sapiens

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<222> (1)..(302)

<223> MAR of chromosome 2 genomic contig; 66958350..66958651 Seite 213

SEL PCT 012.ST25

<210> 237

<211> 651

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<222> (1)..(651)

<223> MAR of chromosome 2 genomic contig; 68307125..68307775

SEL PCT 012.ST25

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<212> DNA

<213> Homo sapiens

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<222> (1)..(367)

<223> MAR of chromosome 2 genomic contig; 68308243..68308609

<400> 238

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<212> DNA

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<222> (1)..(499)

<223> MAR of chromosome 2 genomic contig; 410241..410739

<400> 239

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<211> 402

<212> DNA

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SEL PCT 012.ST25

<222> (1)..(402)

<223> MAR of chromosome 2 genomic contig; 31531..31932

<400> 240

<210> 241

<211> 421

<212> DNA

<213> Homo sapiens

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<221> misc binding

<222> (1)..(421)

<223> MAR of chromosome 2 genomic contig; 32415..32835

<400> 241

ataaatattt tatatataat atataatata tatactatat tatatgitat atatactatt 60
ataatatata taatatata attatatatt atatatacta tlattatata tgatactatt 120

atatattaat ataattatat ataatatata tattatataa tatactatta tatattatat 180

SEL PCT 012.ST25

ataatagtat attatataat atatatatta tatataatag tattatatat actattatat	240
attatatata tiatatatat ataaaatata atataatata tataatatat aatattaata	300
ttatatatat aatataatat aatatataat ataatataat atatatatta ataaaattat	360
attaatatat aatatataat agtatattat atacatatat aatatataca atatataata	a 420
t 421	